

Exhibit HH

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 21-888
Zimulti (rimonabant)
Sanofi-Aventis

Wednesday, June 13, 2007

8:00 a.m.

Hilton Silver Spring
8727 Colesville Road
Silver Spring, MD

PARTICIPANTS

Clifford J. Rosen M.D., , Acting Chair
LCDR Cathy A. Miller, MPH, Executive Secretary

EMDAC Members (Voting)

Kenneth D. Burman, M.D.
Thomas O. Carpenter, M.D.
Katherine M. Flegal, Ph.D.
Jessica W. Henderson, Ph.D.
Michael A. Proschan, Ph.D.

Temporary Members (Voting)

Melanie Coffin
Dominic A. Ciraulo, M.D.
Sid Gilman, M.D., FRCP
Wayne A. Goodman, M.D.
Jules Hirsch, M.D.
Robert A. Kreisberg, M.D.
Phillip S. Wang, M.D., Ph.D.
Paul D. Woolf, M.D.

Industry Representative (Non-Voting)
Steven W. Ryder, M.D.

FDA Participants (Non-Voting)

Mary H. Parks, M.D.
Eric G. Colman, M.D.
Karen Davis-Bruno, Ph.D.
Curtis Rosebraugh, M.D.
Amy G. Egan, M.D., MPH

3

C O N T E N T S

Call to Order	
Clifford J. Rosen, M.D.	5
Introductions	6
Conflict of Interest Statement	
LCDR Cathy A. Miller, MPH	8
Introduction/Background	
Eric G. Colman, M.D.	10
Guest Speaker Presentation	
Kelly Posner, Ph.D.	15
SPONSOR PRESENTATION--SANOFI-AVENTIS	
Introduction	
Richard Gural, Ph.D.	36
Mechanism of Action	
Kenneth P. Mackie, M.D.	49
Medical Need and the Clinical Efficacy of Rimonabant	
Pierre Rosenzweig, M.D.	69
Clinical Safety of Rimonabant	
Paul Chew, M.D.	93
Proposed Risk Management Plan	
Richard Gural, Ph.D.	140
Benefit/Risk of Rimonabant	
Louis Aronne, M.D.	158
Clarifying Questions from the Committee	170
FDA PRESENTATIONS	
Preclinical Evaluation of Rimonabant	
Karen Davis-Bruno, Ph.D.	185
Clarifying Questions from the Committee	215

C O N T E N T S (Continued)

Open Public Hearing

1. Sidney M. Wolfe, M.D. 223
Director, Public Citizen's
Health Research Group
2. Lynn McAfee 235
Director, Medical Advocacy
Council on Size and
Weight Discrimination
3. Caroline M. Apovian, N.D. 243
Secretary/Treasurer,
The Obesity Society

FDA PRESENTATIONS [Continued]

- Clinical Efficacy and Safety of Rimonabant 251
Amy Egan, M.D. MPH
- Committee Discussion and Questions 328

P R O C E E D I N G S

Call to Order

DR. ROSEN: Good morning and welcome to the Endocrinologic and Metabolic Drugs Advisory Committee Meeting. I am Dr. Clifford Rosen and I am the Acting Chair of this Committee.

We have a full agenda and a full room, so we are going to try to stick to our schedules. I am going to start first by providing an introduction for each of the members who will go around the room.

Before that, I need to read something. Today's meeting will have a lot of discussion, which will result in recommendations at the end of the day for the FDA. We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing details of this meeting with the media until its conclusion.

I would like to start by brief introductions around the room, so everybody is familiar with the people on the Committee. I would

like to start with Dr. Parks on the righthand side and we will move counterclockwise.

Introductions

DR. ROSEBRAUGH: Dr. Parks has instructed me to start, so I always do what she says. I am Curt Rosebraugh. I am the Deputy Director of the Office of Drug Evaluation II.

DR. PARKS: I am Dr. Mary Parks, Director, Division of Metabolism and Endocrinology.

DR. COLMAN: I am Eric Colman, Deputy Director, Metabolism and Endocrinology.

DR. EGAN: I am Amy Egan, medical reviewer.

DR. DAVIS-BRUNO: I am Karen Davis-Bruno, Supervisory Pharmacologist, Division of Endocrine and Metabolism.

DR. WOOLF: I am Paul Woolf, Chairman of Medicine, Crozer-Chester Medical Center in suburban Philadelphia.

DR. HIRSCH: Jules Hirsch, Professor Emeritus at Rockefeller University.

DR. GILMAN: Sid Gilman, Professor of

Neurology, University of Michigan Medical Center.

LCDR MILLER: Cathy Miller, FDA Advisors
and Consultants Staff.

DR. ROSEN: Clifford Rosen, Senior
Scientist at the Jackson Laboratory.

DR. KREISBERG: Bob Kreisberg, Birmingham,
Alabama.

DR. CIRAULO: Domenic Ciraulo, Chairman of
Psychiatry at Boston University School of Medicine.

MS. COFFIN: Melanie Coffin, Patient
Representative.

DR. WANG: I am Philip Wang. I am the
Director of the Division of Services and
Intervention Research at the National Institute of
Mental Health.

DR. GOODMAN: Wayne Goodman, Chairman of
Psychiatry at the University of Florida.

DR. PROSCHAN: Mike Proschan. I am a
statistician at NIAID.

DR. FLEGAL: Katherine Flegal from the
Centers for Disease Control and Prevention.

DR. HENDERSON: Jessica Henderson. I am

the Consumer Reviewer.

DR. CARPENTER: Tom Carpenter, Pediatric Endocrinology, Yale University.

DR. BURMAN: Ken Burman, head of Endocrine at the Washington Hospital Center.

DR. RYDER: Steve Ryder, Pfizer R&D, Non-Voting Industry Rep.

DR. ROSEN: Thank you, Steve.

The agenda will be as previously published. We will have three people speaking at the open public hearing starting at 1:00 p.m.

Cathy has a Conflict of Interest Statement.

Conflict of Interest Statement

LCDR MILLER: The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the agenda for today's meeting and all financial interests reported by the members and consultants, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note that Dr. Steven Ryder is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry.

Dr. Ryder's role on this committee is to represent industry interests in general and not any one particular company.

Dr. Ryder is employed by Pfizer. Pfizer makes a competing product to Zimulti.

We would also like to note that Dr. Kelly Posner has been asked by the FDA to participate in this meeting as a guest speaker. Dr. Posner is employed by the New York State Psychiatric Institute's Department of Child Psychiatry.

Dr. Posner reports that she has had research support from Sanofi-Aventis, the sponsor of Zimulti, and three of its competitors, Abbott Laboratories, GlaxoSmithKline and Novartis.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to

exclude themselves from the discussion and their exclusion will be noted for the record.

With respect to all other participants, we ask that in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. ROSEN: Okay. We are going to have Dr. Eric Colman give a brief introduction and overview, and also a presentation.

Introduction/Background

DR. COLMAN: Thank you, Cliff.

We have a fairly full agenda today, so I will try to keep these comments to a minimum. First, I would like to thank Dr. Rosen for agreeing to serve as Chair on this meeting. I would also like to thank the standing and temporary committee members for making a commitment and being here today. It is very important to us.

As you know, we are going to be talking about rimonabant today. This is a first in class

cannabinoid I receptor antagonist/inverse agonist.

The focus today is on rimonabant's use as a weight management product, specifically, its efficacy and safety when used as a weight management product.

The target population is individuals who are obese and moderately overweight. Dr. Kelly Posner will begin this morning's presentations with a summary and overview of the Columbia Classification algorithm of suicide assessment. Her talk will orient us for later discussions about the relationship between rimonabant, depression and suicide, suicidality obviously a big concern for us.

Following that, Sanofi has a series of presentations ranging from mechanism of action to a proposed risk management plan, and then we will complete the morning session with a presentation by Dr. Karen Davis-Bruno, a pharmacologist from the FDA, who will give us thoughts on the preclinical evaluation of rimonabant.

Following the lunch break, we will have the open public hearing and then we will have the

final presentation of the day by Dr. Amy Egan, FDA Medical Officer, who will be discussing for the most part some key safety issues and concerns with rimonabant.

If we keep to the schedule, we should have about two and a half hours for discussion. Let me remind you of the issues, the point of discussion, and the questions that we will be asking the Committee to address towards the end of the meeting.

The first point of discussion is a request to please discuss your level of concern regarding rimonabant and psychiatric events, in particular depression and suicidality and neurological adverse events, in particular seizures, and the reasons behind your thinking on these issues.

A question that we will be asking you, do you believe that the currently available data sufficiently characterize rimonabant's safety profile and, if no, please discuss what additional data should be obtained.

The third question reads as follows:

Based on the currently available data, do you believe that rimonabant has a favorable risk-benefit profile and should be approved for the indication of weight management in individuals with a body mass index of greater or equal to 30 and greater than 27 when accompanied by at least one comorbid condition.

Again, if the answer is no, please explain why and discuss what additional information the sponsor could obtain that might improve rimonabant's risk-benefit profile.

Again, on behalf of the Division and the Agency, I would like to thank all of the Committee members and our guest speaker for taking the time and energy to be here today for this meeting, which I think we all agree is a very important meeting.

DR. ROSEN: Eric, are you going to present the plaques to the people who are departing, or Kelly? Okay.

DR. PARKS: This year, as some of you may know, four of our members on the Endocrine and Metabolic Drugs Advisory Committee will be

retiring.

Present with us today are two of them, Drs. Thomas Carpenter, pediatric endocrinologist who has been with the Committee since July of 2003, and Dr. Steven Ryder, Industry Representative, who has been with the Committee since February of 2004.

We would like to express our great appreciation for their contributions over the years to many, many advisory committees and their expertise. We look forward to further communication and collaboration with them over the years.

Thank you very much.

[Applause.]

DR. ROSEN: My thanks as well for coming to the last meeting, last and very important meeting.

Thank you, Dr. Parks.

I think we will start with Dr. Posner, who will present the guest speaker presentation on suicidal issues. She is from the Department of Child Psychiatry at the New York State Psychiatric

Institute in New York.

Welcome, Dr. Posner.

Guest Speaker Presentation

Suicidality Issues in Clinical Trials

Columbia Suicidal Adverse Event

Identification in FDA Safety Analysis

DR. POSNER: Thank you. Good morning,
everybody.

[Slide.]

As mentioned, I am here to give you some
perspective and clarification on what we mean by
suicidality in this context.

[Slide.]

I just wanted to take a moment to clarify
my disclosures. All the original work that I am
going to be describing was commissioned and funded
by FDA only. Subsequently, we had research support
from numerous pharmaceutical companies through
Columbia and RFMH only to help execute FDA's
suicidality classification mandates and have never
taken any personal compensation or support.

[Slide.]

My classification co-investigators, Dr. Oquendo, Dr. Gould and Dr. Stanley, I would like to thank for all their work, and I will be talking about a prospective scale that I am going to go into more detail, as well as the contributors to that.

[Slide.]

Where does this suicidality issue, where did it all begin? Well, the problem is in the field of medicine and even in psychiatry, we are challenged by a lack of clarity about how to define even the most basic suicidal behaviors and corresponding to that, we have no well-defined terminology. This cuts across clinical and research settings.

What happens is this lack of systematic or standardized language really shows itself very much across all clinical trials and what we see is the same behavior or the same event is called 10 different things - attempt, non-attempt, threat, gesture. They are often pejorative and they are based on incorrect notions about the relationship

between seriousness and lethality.

[Slide.]

So, what that leads to is difficulty in interpreting the meaning of reported adverse events that occurred in any of the controlled trials. What happens is that adverse events that should have been called suicidal may have been missed, and adverse events that may have been inappropriately classified as suicidal.

[Slide.]

Now, these are real examples. This whole story began, as many of you know, with the pediatric antidepressant story and these are real examples of the difficulties that I am talking about in adverse event labeling.

These came from the pediatric clinical trials. So, the first one, 10-year-old male exhibited symptoms of personality disorder. One day later patient attempted to hang himself with a rope after a dispute with his father, yet the preferred term was "personality disorder," nowhere is suicidality indicated.

The overdose of 6 capsules was in fact intentional, yet called accidental overdose and neurosis.

Patient took 11 tablets, called medication error. One of my favorites, before his mother is called to the site, he wrapped a cord from the mini-blinds around his neck, called hostility.

[Slide.]

If you have been following this, we call this the "slap heard around the world," because it has been written about a lot when these issues are discussed. Somebody somewhere called a slap in the face a suicide attempt and the update said, my God, how can we have such an important safety analysis with data that is not interpretable.

What is really interesting to note is that the severity goes both ways. It is not just pharmaceutical companies calling things less severe than they should be. They are calling a lot of things more severe than they should be because there is no training and there is no systematization, and nobody knows how to do this

the right way.

So, after we did the pediatric trials, the system was mandated across, you know, antidepressants, anticonvulsants, et cetera, so we have seen thousands and thousands of adult examples, and I can tell you the problems are very much as apparent.

So, this is an example of an adult case. Patient made attempt to stab himself in the abdomen, which resulted in minor injury only. This was not considered a true suicide attempt and no action was taken, not significantly significant, called trauma.

[Slide.]

So, what do we need to do to address this problem? Well, Columbia was commissioned by FDA, and we knew we had to apply a common set of guidelines. We needed to speak the same language across all these trials and, of course, we needed to look consistently. And we wanted to have a meaningful language, of course. So we developed what was the most research-supported approach and

that is called the Columbia Classification Algorithm for Suicide Assessment which, as you know, is the system that was used with the data today.

[Slide.]

Now, what were we actually classifying in these trials or any of the others? What happened is the FDA asked the companies to do electronic text string searches of their databases, so you can see the terms there "suicide" or "overdose" attempt, cut, hang, gas, et cetera. And anytime an adverse event term with one of those terms came up, they were supposed to flag it and write a narrative about it.

They were permitted exclusions for events that represented obvious false positives like "gas" and "gastrointestinal." But, you know, when we saw all the variability of the labeling, the first time around we said, you know, we really should broaden the search to make sure no suicidal events were missed, and then ask for all accidental injuries, all serious adverse events, and all deaths, which

is what was done here, as well.

So, then, the companies constructed narratives of those events and sent them blinded to us for classification.

[Slide.]

Now, when I say "blinded," of course, we wanted to have the most conservative, unbiased approach possible, so any company, any study, all these things are blinded, drug name, company name, patient ID numbers, obviously, active or placebo arm, but even any and all medication names and types, because it may be that some meds are associated with a particular side effect profile and thus could potentially bias something.

Of course, we blinded those labels that had been given originally by the investigators. Okay. So, that is what we did.

[Slide.]

What is this scheme? The primary thing that we needed to do for FDA and for these studies was separate suicidal events from non-suicidal events.

So, those blue boxes are what went into every primary analysis, suicidality analysis, whether it was this or the antidepressant, and what we mean by what we think are suicidal is completed suicide, suicide attempt, suicidal ideation, and preparation behaviors.

But as you know, these studies weren't set up to assess for suicidality, so we had to have some other classifications to put the events in that could have been suicidal. But we just didn't have enough information.

You can see self-injurious behavior with unknown intent. There may have been narratives that said patient cut wrist, and they may have been cutting their wrist because they were trying to kill themselves or they may have been cutting their wrist because they were self-mutilating and trying to feel better, we just didn't know.

So, that is what we call the worst case sensitivity analysis, you know, where there was not enough information. But they may have been

suicidal.

[Slide.]

These are the codes that were used here and everywhere else. And you can see the 1 through 4 are all the primary suicidality codes and then they go down in order of severity in terms of not enough information and then all the others that have nothing to do with suicidality.

[Slide.]

I am not going to go into every definition. But the whole scale, the whole system was really very much driven by the definition of suicide attempt, and this comes from Dr. Mann's scale, the Columbia Suicide History form. At Columbia, 20 years of research support doing it this way. As I said, we went for the most research-supported thing that we could get.

What we mean by suicide attempt is a self-injurious act committed with at least some intent to die, as a result of the act.

The first thing to note, it is a self-injurious act, there does not have to be any

injury or harm, just the potential for it. So, the guy puts a gun in his mouth, pulls the trigger and, fortuitously, the gun fails to fire. It is still a suicide attempt even though there is no injury.

These are the common misperceptions that lead people to call things by the wrong names.

Non-zero intent, often people have mixed motives when they are dealing with suicidality, so only a piece of them should have wanted to kill themselves when they were engaging in this behavior and that is enough to call it suicidal. Intent can be inferred from circumstances or it can be explicit obviously.

[Slide.]

Suicidal ideation definition. This is thoughts of wanting to be dead, wanting to die or ending one's life. Very clearly, it has no behavior associated with it. It is just a thought. For example, following a fight with her boyfriend, patient thought about taking an overdose to end her life.

Patient was feeling depressed and thought

his bad luck would never change and wished he were dead.

[Slide.]

So, what were our findings? The C-CASA findings, which are about to come out in the American Journal of Psychiatry, were very interesting.

What we found is remember we broadened the search to make sure nothing was missed. We found more suicidal events overall, so it was well worth going through, looking through the accidental injuries and things. But fewer events were labeled suicide attempt.

In the antidepressant analysis, 50 percent of the cases were not called suicide attempts. The pharmaceutical companies called 45 cases suicide attempts that we thought shouldn't be called suicide attempts, really decreasing the harm ratio dramatically.

We had excellent reliability. FDA did an independent audit. They called C-CASA robust and reproducible, demonstrating excellent

transportability for situations like we are in today.

What is really interesting is that there was an analysis in the pediatric antidepressant trials that relied just on the pharmaceutical company labels before we applied this system and, when you compare the two findings, they were made up of one-third different cases, so people said, well, there were similar results. But they were actually made up of different patients, really confirming the reason for having done this.

[Slide.]

Furthermore, the safety analysis using this system had more precise estimates of risk and tighter confidence intervals compared to the prior analysis that relied on the sponsor ratings, also reduced estimates of risk.

This is consistent with previous findings that misclassification leads to overestimation of true risk.

[Slide.]

So, we did the best we could with limited

data and I want to spend a moment talking about what the limitations of this data actually are, because I think it is very critical to the discussion today.

As I said, these studies were not designed to assess for suicidality. These studies, the antidepressant studies even were not. Association does not mean causality. Just because we see this association, it does not mean that the drug is necessarily causing the association.

There has been a lot of discussion through the years and in other settings that what is a very plausible alternative explanation to this causal link, well, it is something called ascertainment bias.

When people are on active medication, they have more side effects - headache, stomachache, et cetera. They may just have had more contact with their provider to hear about a suicidal occurrence as opposed to it being a true difference in risk. And the only way you can end up knowing that that is the case is by having prospective future

systematic monitoring, so that is one alternative explanation that may account for the differential among drug and placebo in all of these safety analyses.

[Slide.]

Now, just to support that theory, first, in the pediatric analyses, they did have some systematic data, so depression scales were collected in most of those pediatric trials, Hamilton Depression Rating Scale, et cetera, and FDA did an analysis of the suicide item data, systematic suicide item data, and it did not confirm the risk.

So, when you looked systematically, it did not show a signal. But, when you looked at the spontaneous adverse events, it did show a signal. And there are many analyses since then that have shown this kind of confusing and compelling discrepancy, meaning that it is possible that these adverse-event data are somewhat misleading or false. We just don't know; right? We have reason to question.

[Slide.]

How do we think we fix the problem?

Systematic administration of a tool designed to track suicidal events across a treatment trial. This Columbia Suicide Severity Rating Scale is the prospective version of the C-CASA system that we developed for FDA, and this is the way to get better safety monitoring and avoid inconclusive results.

I just wanted to say also that on the first slide, this is a collaboration between a lot of leading experts and Columbia and Pittsburgh and Penn. Dr. Mann is here, one of my lead authors.

[Slide.]

This is the reason why FDA is often recommending it in ongoing and future studies in other areas, as I said, developed by leading experts, very, very evidence based. It is feasible and low burden, typical administration time is not more than five minutes, usually less.

It assesses both behavior and ideation--other scales just look at one or the

other--and it really appropriately assesses and tracks all suicidal events, so we don't call a slap in the face a suicide attempt. We just call the right thing suicidal, and we can control for all those other alternative explanations like ascertainment bias. So, this is better systematic monitoring to give us better answers.

[Slide.]

You can see it gives a study or a person everything we needed to fix the problem - the definition, the probes, the questions, things to allow people to put things in the right boxes, so we can get better safety answers.

[Slide.]

That was behavior.

[Slide.]

This is ideation, operational as the way we have always thought about it from a wish to die through active or planning intent.

[Slide.]

We got together, the authors got together and said what is the minimum amount of information

that one would need in any setting to ask about.

Well, one of those things is lethality, so only when there is an actual attempt does somebody ask about lethality, because it is critical data in a study or any other setting to collect. And then we have other features of ideation, frequency, duration, controllability, et cetera. All these items are significantly predictive of completed suicide. We said what is the minimum amount of information any setting would want to ask about for tracking and severity.

[Slide.]

Various uses. Within a study are multifold treatment benefit outcomes, safety outcomes, clinical safety monitoring. It is coordinated efficiently with other measures. It is easily coupled with inclusion/exclusion. As many of you may know, historically, in studies, in the past, exclusion criteria have been totally arbitrary, serious risk. Nobody knows what that means exactly, so this can help move things in a number of directions.

[Slide.]

Its current use, we have four years of use in clinical trials, large multi-site industry nationally and internationally, a range of therapeutic areas, as you can see, over 20 languages, NIMH trials, surveillance efforts, community clinics.

[Slide.]

In conclusion, intervention trials using prospective and systematic measurement of suicidality would certainly more clearly delineate the relationship between suicidal adverse events and medication treatment.

Consistent assessment can give us more meaningful data, not only within a study, but across studies, improving these pooled analyses for a better understanding about both benefits and safety.

Again, this improved assessment is also critically necessary to better inform risk-benefit analyses, which is why we are all here today.

[Slide.]

Just finally, some perspective on suicidal ideation which will get a lot of attention today. It is very important to remember that suicidal ideation is a symptom of depression. It is a symptom of depression.

Lifetime prevalence of depressive disorders is 29 percent.

A key thing to remember, CDC data, an estimated 10.5 million people will experience suicidal ideation in a year, while 30,000 people will commit suicide. A lot of people will have these thoughts, they are part of depression. It doesn't mean that. It is always very important to keep these numbers in mind.

Thank you.

DR. ROSEN: Dr. Posner, if you would stay around, I would like to ask the committee if they have any questions for Dr. Posner.

DR. PROSCHAN: I was wondering how often you would recommend giving that assessment.

DR. POSNER: Actually, we spend a good bit of time talking to other groups at FDA about

this, and the way we see it and they see it is you give it, every visit, the same way you would give any other rating scale, depression, side effect, or anything.

Otherwise, if you don't, you are just getting back into the same question, the same challenge, not getting optimal data.

DR. ROSEN: I would like to ask is there any specific training necessary for people who are conducting the trials to log onto this or to know exactly what they are asking?

DR. POSNER: The training is very similar to the training of all the other scales that you are familiar with, whether it is ADHD or depression. We go to an investigator, start-up meeting, give the training. We have given, you know, half-hour teleconferences nationally and internationally, usually about 25, 30 minutes.

There are manuals, training tapes.

DR. ROSEN: Is there any hesitancy on the part of the clinical nurse coordinator or the research nurse to provoke or to ask these

questions, or to get that kind of information?

DR. POSNER: My anecdotal experience has been a bit of the opposite. People say uh, finally, something that helps us make sense of this in a better way.

DR. CIRAULO: As you presented that last slide in statistics, that was very helpful. Could you clarify for me what are the data of fleeting suicidal ideation in a general population?

DR. POSNER: Well, you know, I don't think we have very good data about the nuances of ideation like that, frequency, types, et cetera. We do know generally that whether it's a passive wish to die or an active thought, this is the prevalence rate.

So, these kind of measures and things are going to help us get better answers to those questions.

DR. CIRAULO: And this scale would help discriminate the sort of fleeting suicidal ideation which is common in the population?

DR. POSNER: Yes, exactly, so as I said,

it articulates a passive wish to die, you know, a wish to die all the way down to plan and intent, so you can distinguish those things and then get frequency, duration, et cetera, all those features about each one of those things.

It is a good question and I appreciate it.

DR. ROSEN: Other questions or comments from the review panel?

Okay. Thank you, Dr. Posner.

I think we are going to start. We are a little ahead of schedule actually, but we are going to start our sponsor presentation.

The first presentation, the introduction will be Dr. Gural from Sanofi-Aventis. Welcome.

Sponsor Presentation

Sanofi-Aventis

Introduction

DR. GURAL: Good morning, Mr. Chairman.

Members of the Advisory Committee, Food and Drug Administration, consultants and interested parties: I am Richard Gural. I am the Vice President for Drug Development within Scientific

and Medical Affairs within Sanofi, and I will be the moderator today for the company.

We are here to present the results of the clinical studies of rimonabant in the treatment of obesity and type 2 diabetes.

The agency has asked the committee to consider the three questions outlined to you this morning by Dr. Colman and hopefully, we will be providing you information which will allow you to fully deliberate on these questions.

[Slide.]

Our presentation today will include brief introductory remarks made by myself followed by a review of the mechanism of action by Dr. Ken Mackie from the University of Indiana.

The medical need, clinical benefit and efficacy data will be presented by Dr. Rosenzweig of Sanofi-Aventis, followed by a review of the safety by Dr. Paul Chew.

I will then present again a management of the risk of rimonabant followed by the overall clinical benefit by Dr. Lou Aronne.

[Slide.]

Rimonabant has been developed in accordance with both the 1996 and the 2007 guidance documents for the development of drugs for the control of obesity.

These included not only the duration and the size of the study, but also the efficacy criteria. Indeed, we will see that the size of the studies conducted exceeded the number of patients and the duration to be included.

[Slide.]

Also, in these guidance documents, the patient population was clearly identified and we have studied both patients with a BMI greater than 30 kg/m² without comorbidities or 27 kg/m² with comorbidities as identified here.

Also, the 1998 and 2000 guidance documents on the development of drugs for the treatment of obesity has also been followed.

[Slide.]

Now, exactly, what are the studies that we will be reviewing with you today? RIO-North

America, which stands for rimonabant in obesity, was conducted in North America and it had a duration of 1 year on drug followed by re-randomization, the design of which Dr. Rosenzweig will present to you this morning.

Studies were also conducted RIO-Europe, Lipids, and Diabetes. All four of these studies were conducted on a global basis and represent a Phase III development program and were conducted in accordance with the guidance documents.

We also have conducted studies in the treatment of diabetes in patients who have failed or had inadequate control, metformin or sulfonylurea, or in a recently completed study at SERENADE in treatment-naive, type 2 diabetic patients.

[Slide.]

Safety will be one of the key topics that we will discuss today. As you can see from this slide, nearly 7,500 patients were treated with rimonabant at a dose of 20 mg, which is the recommended dose, for a duration between 1 day and

2 years.

The overall patient safety database in the controlled studies during the development is represented here at a number of 15,000. They came from 1,000 or more patients in clinical pharmacology, 1,000 patients in our Phase II program, 5,400 patients from the obesity diabetes program, which will be discussed in greater detail today, and about 7,500 patients from a smoking cessation development program. Dr. Chew will be reviewing all of this data with you today.

[Slide.]

We did not stop there. As you will hear later, rimonabant is currently approved in 37 countries, marketed in 18. So, we have benefit from information that is from our postmarketing surveillance of almost 110,000 patients. We have approximately 14,000 patients from ongoing studies, as well as 15,000 patients from our completed Phase I and Phase III.

This gives a total exposure of database of approximately 140,000 patients.

[Slide.]

We haven't stopped, though. We did not stop at just the development of the drug in the treatment of obesity, we also evaluated, as you can see here, rimonabant in a number of therapeutic indications specifically addressing the potential for prevention of cardiovascular risk.

A currently ongoing study called CRESCENDO, which the FDA referenced in the briefing document, is currently enrolling approximately 8,000 patients out of an anticipated 17,000.

The rest of the studies that are identified here, including RAPSODI in the prevention of type 2 diabetes, have been fully enrolled, and the numbers are represented here. We are continuing to collect the data and that will also be discussed from the safety point of view today.

It gives us the number, as I previously mentioned to you before, of approximately 14,000 patients in our ongoing studies.

[Slide.]

Now, what is Zimulti or rimonabant?

Rimonabant, as you have seen, has been extensively published. It is a selective and neutral antagonist of the CB1 receptor and we will hear later this morning from Dr. Mackie on the characterization of this activity.

Zimulti, in its proposed market image, is a 20 mg tablet intended for once daily administration along with breakfast.

[Slide.]

Just briefly, I would like to summarize some of the hallmarks of the pharmacokinetics of rimonabant. This also has been extensively studied, as you saw in the patients represented during the Phase I trial of approximately 1,000.

The hallmarks of rimonabant pharmacokinetics is that it has good absorption. It is extensively protein bound, approximately 99 percent. It has a modest accumulation on once-a-day administration and a long terminal half-life of 16 days in patients who are obese.

As rimonabant is metabolized, both the

CYP3A4 and amidohydrolases, the effects of the potent inhibitors of the 3A is modest, resulting in approximately a 2.7-fold increase in rimonabant exposure.

Finally, as rimonabant does not inhibit the CYP3A enzymes, drug-drug interactions through these mechanisms are not anticipated.

[Slide.]

Let me just review briefly with you the current regulatory status of rimonabant. As I mentioned before, it is currently approved in 37 countries and marketed in 18. In Europe, the marketing application or the MAA was submitted in April 2005 via the centralized procedure. It was approved in June 2006.

The indication in Europe is as you see here, as an adjunct to diet and exercise in the treatment of obese patients with comorbidities especially that of type 2 diabetes or dyslipidemia.

As you may know, in Europe, when a product is approved via the centralized procedure, it is approved in 25 countries simultaneously, all with

the same label and the same indication, through a patient information leaflet and a package insert known as an SMPC.

Immediately following the approval in June 2006, the product was launched in the UK, and I will be showing you later today some of our experience with that, and we will be discussing that, as well, during the safety presentation.

[Slide.]

Currently, within the EU, a type 2 variation is pending for the treatment of diabetes based on the information that you have also in your dossier today--that is, the RIO-diabetes, as well as the SERENADE studies.

Later today, I will be discussing a Risk Minimization Plan that we will be employing in the United States. I would just like to emphasize that this is not just for the United States. Currently, a Risk Minimization Plan is part of the core risk-benefit that we have for rimonabant, it is being applied in the UK, as well as the rest of Europe, and again I will be showing you some of

that data later today.

[Slide.]

Where are we in the United States? An NDA for rimonabant was submitted in April 2005 using the same data that was submitted in the European Union.

In February of 2006, an approvable letter was obtained from the Division following a number of interactions with the Division where we thoroughly reviewed the approach and the type of data necessary to address the elements of the approvable letter, a complete response was submitted in October 2006.

This response included an updated safety from both the completed and the ongoing studies, as well as most recently information from our experience based on the postmarketing information coming from Europe through a procedure called a PSUR, or a Periodic Safety Update Report.

We reviewed all neurological and psychiatric events and, as you heard from Dr. Posner, we employed the C-CASA as part of the

analysis for suicidality, as well as, you will hear today we are proposing a risk management plan.

During the review of the application, the agency asked for, and we agreed to, a 3-month extension for the review of the file based on the size of the information that is contained within it.

At that time, we took the opportunity to submit the SERENADE data, which had been recently completed during and following the complete response in October, and, of course, today, we are having the Advisory Committee with you here today to review this information.

[Slide.]

Our NDA submission in October contained two indications. It contained an indication in the treatment of obesity, as identified here, as well as use in patients in combination with metformin or sulfonylurea who have not had adequate control.

[Slide.]

We will hear a lot today about the safety of rimonabant. We will hear a lot about the

efficacy of rimonabant. But who is the right patient to receive rimonabant? Not everybody.

Rimonabant is intended to be used in patients with a BMI greater than 27 kg/m² with at least one cardiovascular metabolic risk factor and/or a BMI greater than 30 without any of the comorbidities.

Since obesity is indeed a chronic disease, long-term administration is recommended for rimonabant. We will hear a lot about the safety, so it is important to note now who is not the right patient to be administered rimonabant.

Who is not appropriate is a patient with the past history of depressive disorders and/or suicidality, or patients with a diagnosis of depressive disorders, or patients currently under antidepressant therapy.

We will also have a discussion today about seizures. You will see that we are also recommending that the appropriate patient not to receive rimonabant will be one who is on current anti-epileptic therapy.

So, the right patients are those for which the indication is sought. The inappropriate patients are those who have depressive episodes in the past, or currently on it, or those who are currently receiving anti-epileptic therapy.

[Slide.]

With us today, we have a number of consultants and experts. These experts and consultants have participated with us both in the development of rimonabant and in preparation for the Advisory Committee today.

They include experts in the area of mechanism of action, endocrinology. Many of these names are familiar to many of us. Internal Medicine.

[Slide.]

And because of the unique nature of rimonabant in Psychiatry.

[Slide.]

And Neurology. Also, the risk management plan has been thoroughly reviewed with the Epidemiology and statistical support.

[Slide.]

Now, it will be my pleasure to introduce Dr. Ken Mackie, who is Professor and the Chairman of Neuroscience at Indiana University and the Linda and Jack Gill Chair.

Dr. Mackie has published extensively in the field of endocannabinoid receptors and is dealing with the mechanism of action for rimonabant.

Dr. Mackie.

Mechanism of Action

DR. MACKIE: Thank you, Dr. Gural.

[Slide.]

Good morning, Mr. Chairman, members of the Committee, ladies and gentlemen, I would like to give you an overview of the mechanism of action of rimonabant today with an eye towards its clinical efficacy and potential safety concerns.

[Slide.]

My talk will cover four points. First, I will briefly introduce endocannabinoid system, then, I will talk about the pharmacological

properties of rimonabant relevant to its mechanism of action, present evidence for the hyperactivity of the endocannabinoid system in obesity and type 2 diabetes and then, finally, I will present preclinical data providing the rationale for the therapeutic use of rimonabant in treatment of obesity and type 2 diabetes.

[Slide.]

The modern era of cannabinoid research and the discovery of the endocannabinoid system really dates back to 1964 with the discovery of delta-9 THC as the primary psychoactive constituent of cannabis by Raphael Mechoulam and his group.

This was followed by a period of productive research, culminating in the cloning of CB1 and CB2 receptors, as well as the discovery of their endogenous ligands, endocannabinoids, and anandamide, and 2-arachidonoylglycerol

An important distinction between endocannabinoids and the more classical neurotransmitters like glutamate and acetylcholine is that they are not synthesized ahead of time and

stored in vesicles; rather, they exist in new membrane as preformed lipid precursors and are made on demand by specific enzymes following specific stimuli.

Together, it is the endocannabinoids, the cannabinoid receptors, and their synthesizing and degrading enzymes that comprise the endocannabinoid system.

A variety of evidence suggests that the endocannabinoid system exists to fine-tune various physiological processes, sort of running in the background you might think of it. However, it can be detrimental when it is overstimulated in certain diseases, such as obesity.

Key to today's discussion is that rimonabant, the first CB1 receptor selective antagonist was developed in 1994.

[Slide.]

CB1 receptors are widespread throughout the brain including cortex, amygdala, basal ganglia and hypothalamus, which isn't shown in this section, in the brain is present on subpopulations

of both excitatory and inhibitory neurons thus predicting a priori defective cannabinoid receptor activation of blockade is rather problematic.

It is also found in peripheral nerves including those that innervate the gut and help to control the sensations of satiety.

Surprisingly, to those of us who came to the cannabinoid field from neuroscience was demonstration of cannabinoid receptors on a variety of peripheral tissues including adipocytes, liver, and skeletal muscle.

In many of these tissues, CB1 receptor levels are regulated during pathological conditions such as cirrhosis and obesity.

[Slide.]

Rimonabant was discovered to be a high-affinity CB1 receptor antagonist blocking the effects of THC and other cannabinoids both in vivo and in vitro.

An important consideration for any antagonist is its selectivity. As can be seen in this binding experiment shown on the left here,

rimonabant has a high affinity for CB1 receptors and a relatively low or very low affinity for CB2 receptors, the most closely related other GPCR coupler receptor.

Endocannabinoids interact with a number of other proteins and ion channels. As listed in the table to the right are some of the more prominent receptors and ion channels that endocannabinoids interact with, and you can see that rimonabant has a very, very low affinity for any of these compared to the CB1 receptor.

Not shown here on the chart, but mentioned in FDA's presentation is A1 adenosine receptors, I would like to comment that rimonabant has an affinity of greater than 10 micromolar for A1 receptors.

[Slide.]

Rimonabant is an inverse agonist, a term that may be unfamiliar to some of you. On the next two slides we will consider what an inverse agonist is and its implications for rimonabant's pharmacology.

[Slide.]

Shown on the left here in yellow is the behavior of a classic neutral antagonist, which merely prevents agonists from binding to the receptor. If applied to a system that is maximally stimulated here, you can see increasing concentrations of neutral antagonists eventually reverse the response, bringing it down to the baseline level.

However, the pharmacology of many antagonists in clinical use, for example, metoprolol and losartan, cannot be explained by simple neutral antagonism, thus, the concept of inverse agonism has been developed.

It is important to emphasize that inverse agonists are not an exotic species. It has been estimated that 85 percent of G-protein coupled receptor antagonists are actually inverse agonists.

Typically, for an inverse agonism to be detectable, a receptor must have a level of constitutive activity. That is shown here on these two lower curves, so this is the baseline activity

in the resting state.

Increasing concentrations of inverse agonists will drive that level to less than zero. It is very important to realize, though, that just like with agonists, inverse agonists can have differing potencies, as well as efficacies, so inverse agonism is not a black and white property. It is very graded response.

Particularly key is the concentration over which you see neutral antagonism for an inverse agonist versus true inverse agonist effect, which we will revisit later.

One way of thinking of inverse agonists is the binding of inverse agonists can be thought to lock the receptor in an inactive state.

The take-home message for this slide is the important distinction between antagonist and inverse agonist effects is that in the absence of agonist, a neutral antagonist will have no effects, while inverse agonists may have unintended or unexpected effects.

[Slide.]

Does rimonabant behave as inverse agonists? One way to see if an antagonist shows inverse agonist is an artificial system where you have expressed receptors at a very high level in a cell line. But a moralistic situation is to use natively expressed receptors.

This is one such experiment using CB1 receptors expressed in natively expressed cerebellar membranes. The orange curve shows that in the absence of an agonist, increasing concentrations of rimonabant do not inactivate the CB1 receptors shown by no change in GBMS binding, which is a measure of global G-protein activity.

Only when you get up in very high concentrations of rimonabant, greater than a micromolar, do you see inverse agonism.

You will see throughout my slides SR141716, which was the developmental name for rimonabant. However, if you stimulate CB1 receptors with anandamide and then treat them with increasing concentrations of rimonabant here, you can see the classic neutral antagonism that appears

well before inverse agonism.

Just to provide a frame of reference, the steady state trough concentrations of rimonabant in the human studies is about 200 nanomolar, which would put it in this range here, clearly below the range that you see inverse agonism.

Therefore, rimonabant acts as a neutral antagonist at CB1 receptors in clinically encountered concentrations. Thus, as it will be used clinically, it will likely have an effect only in the presence of endogenous cannabinoid tone.

In more complex systems, it is difficult to determine if a change in response seen when giving an inverse agonism is due to true inverse agonism or merely antagonism of endogenous tone.

The only way to determine this unequivocally for CB1 receptors is to prevent endocannabinoid synthesis and we just don't have the tools to do that currently. Nonetheless, in many in vitro and in vivo models, the efficacion rimonabant is neutral.

An example of relevant for potential

adverse effects is shown in this slide looking at excitatory corticosteroidal transmission. A common action of cannabinoids including the endocannabinoids is to inhibit neurotransmission.

Here, the amount of neurotransmitter release is indicated by the dots. You can see the application of a synthetic cannabinoid in this experiment decreases the amount of glutamate release, so decreases glutamate neurotransmission.

Now, if rimonabant was acting as an inverse agonist in this system, you would expect to see an increase in neurotransmission when it is applied, however, you do not see that. Instead, what you see is just neutral antagonism of the synthetic cannabinoid applied here.

Again, in this system, which is a little bit more complex, it behaves as a neutral antagonist. This is still only slice experiments.

What about animals? There is limited sort of global animal data but a very interesting paper that was recently presented looked at the effects of rimonabant on cerebral blood flow in awake

animals using fMRI and, in those studies, while rimonabant blocked the increase in cerebral blood flow seen with cannabinoids, by itself, it has no effect.

[Slide.]

So the endocannabinoid system is here, and those of us who work and enjoy, is involved in many processes. Some of these effects are mediated by CB1 receptors, but it is very important to appreciate that many of them are mediated by non-CB1 mechanisms.

A few of those non-CB1 mechanisms are shown here including CB2 receptors, GPR55, the abnormal cannabidiol receptor, TRPV1 channels and serotonin 5HC3 channels.

So, some of the endocannabinoid mediator processes that have a prominent non-CB1 component, that are relevant to today's discussions are analgesia, amelioration of neural inflammation, such as MS, bone remodeling and control of vascular tone.

The multiplicity of endocannabinoid

actions is complex. Perhaps a useful analogy for thinking of it is epinephrine and beta blockers. While beta blockers will attenuate the chronotropic effects of epinephrine mediated by beta1 receptors, they will have no effect on the vasoconstriction mediated by alpha receptors.

Similarly, blocking CB1 receptors does not antagonize all endocannabinoid signaling. Thus, it is important to appreciate that if activating the endocannabinoid system is beneficial, antagonizing it with CB1 blockade is not necessarily detrimental.

In addition, another noteworthy point is the effects of chronic CB1 blockade are sometimes the exact opposite of acute CB1 blockade, presumably due to slowly developing changes, such as the question of inflammation.

An example of this are neuropathic inflammatory pain models where acute administration of rimonabant causes hyperalgesia, yet, chronic administration of rimonabant is analgesic.

Thus, care must be used in extending

animal studies investigating the acute effects of rimonabant to the human situation where the drug is dosed chronically.

[Slide.]

So, let's change direction now a little bit and look at the role of endocannabinoid system in obesity. It has been known for some years now that activation of the central endocannabinoid system, acting both in the hypothalamus and limbic forebrain, increases food intake and promotes weight gain.

However, recent evidence has emerged suggesting that the peripheral endocannabinoid system is a key player in human obesity.

As shown on the left, circulating levels of two endocannabinoids, anandamide and 2-arachidonoylglycerol, are increased in obese compared to lean women. The middle slide shows that if you break down the type of obesity between primarily visceral fat to subcutaneous fat, levels of circulating are even more increased in subjects with visceral obesity.

Finally, moving to type 2 diabetes, in subjects that are matched for age and BMI, but have type 2 diabetes, both anandamide and 2-arachidonoylglycerol levels are increased, suggesting that across both obesity and type 2 diabetes of the endocannabinoid system is overactivated.

[Slide.]

So, additional evidence for the role of overactivated endocannabinoid system and obesity comes from population studies. Fatty acid aminohydrolase, shown here as a crystal structure, is the primary enzyme that degrades anandamide.

A mutation here, proline 3 at 129 decreases the enzyme activity by decreasing stability and decreasing enzyme levels, which results in a decrease in activity, which is shown here, looking at enzyme activity in lymphocytes from patients with this mutation.

This is a naturally occurring mutation, relatively low percentage of the population. But you can see that there is an association of this

polymorphism with obesity shown here for caucasian Americans, but also in the African-American U.S. population.

[Slide.]

So, a number of preclinical studies have shown that the reduction of food intake with rimonabant is transient, returning towards baseline levels after days or a few weeks.

Despite the transient reduction energy intake, weight loss is consistently found to be sustained, suggesting that weight loss is due to additional metabolic mechanisms.

An example here is an experiment where mice made obese by diet were treated either with vehicle or 10 mg/day of rimonabant. And you can see, over the course of 4 weeks, they lost approximately 20 percent of their body weight.

As one measure whether this is purely mediated through decreased food intake, a control group that was fed the same amount of calories as the high fat diet mice and studied at the same time only lost about two-thirds of that weight, or about

14 percent.

These results strongly support an effect of rimonabant on body weight that goes beyond the reduction of food intake. But this is a true peripheral effect or mediated by the CNS.

[Slide.]

Evidence for a peripheral set of action comes from this experiment. On the left panel is shown an experiment where cultured adipocytes were incubated with rimonabant, which increased the level of adiptonectin mRNA expression in a time-dependent fashion.

A longer term experiment is shown on the right looking at secreted adiptonectin in the media where cultures are treated for 4 days with rimonabant at these 2 concentrations. And you can see that this treatment results in a fairly marked increase in secreted adiptonectin.

So, these results show that rimonabant stimulates both adiptonectin mRNA expression and protein secretion and adiposed cells in culture clearly a system totally devoid of any CNS

influence.

So, what significance these find is demonstration of functional endocannabinoid system solely in a peripheral tissue. Moreover, the established role of adiptonectin on lipid metabolism and influence sensitivity provides a plausible biological basis for some of the clinical effects of rimonabant that we will hear about later.

[Slide.]

So, animal studies are useful for looking at mechanism, but can they inform us at all about outcome? in this experiment, Zucker rats defective in leptin were studied. The leptin deficiency leads to hyperphasia, obesity, dyslipidemia, type 2 diabetes, chronic renal failure culminating in an early death.

In these experiments, four groups were used. Obese rats, shown in red here, obese rats that were treated with rimonabant, shown in yellow, obese rats that were pair fed the same amount of calories as rimonabant to get an idea of caloric

restriction, and then, as a control, lean heterozygous animals which still have leptin.

In this experiment, treatment began at 12 weeks, shown here, so when they are 12 weeks of age, it corresponds to zero time in the experiment--and then just followed for the next year.

Starting at 9 months, here with the untreated obese rats, the early mortality becomes apparent. By 12 months, only 40 percent of the obese non-treated rats were alive, while about 80 percent of the obese-treated rats were still alive.

Of note, none of the rimonabant treated rats over this long-term study had seizures.

Correspondingly, the rimonabant group showed an improvement versus a vehicle-treated obese rats in most metabolic primers related to glucose metabolism, lipids, inflammation and renal function.

Thus, rimonabant treatment in this rat model of obesity clearly improved survival.

[Slide.]

To sum up the preceding slides and studies, unfortunately, I didn't have time to present, this is a schematic view of a current understanding of the mechanism of action of rimonabant in decreasing body weight. Rimonabant decreases food intake both through central actions in hypothalamus and limbic forebrains, and by significant peripheral actions on sensory nerves innervating the gut.

It also acts on peripheral tissues including adipose tissue, liver, skeletal muscle and gut. The culmination of these actions is to decrease food intake and decrease fat storage. This dual mode of action both central and peripheral contributes to the observed metabolic effects of rimonabant including improved insulin resistance, increased HDL cholesterol, decreased triglycerides, increased glucose uptake and increased adiponectin.

[Slide.]

To summarize, the endocannabinoid system is an endogenous physiological system which

integrates nutrient intake, metabolism and energy storage.

At clinically relevant concentrations, rimonabant acts as a neutral antagonist of the CB1 receptor.

Chronic overactivation of endocannabinoid system is associated with obesity and type 2 diabetes. Rimonabant decreases body weight, in effect partially explained by reduced food intake and increases adiponectin, suggesting that it may have beneficial metabolic effects.

Chronic rimonabant treatment improves metabolic parameters and survival in a rat model of obesity.

Thus, the CB1 receptor antagonist is a valid therapeutic target for the treatment of obesity and type 2 diabetes. So, the next step was to assess if rimonabant would have the same beneficial effects in humans.

Thank you.

[Slide.]

DR. GURAL: Thank you, Dr. Mackie.

I would like to now introduce Dr. Pierre Rosenzweig, Vice President of Internal Medicine and Clinical Development with Sanofi-Aventis.

Dr. Rosenzweig will present on the medical need and the clinical efficacy of rimonabant.

Dr. Rosenzweig.

Medical Need and Clinical Efficacy of Rimonabant

DR. ROSENZWEIG: Good morning, Mr. Chairman, members of the Committee.

[Slide.]

After reviewing the medical need, I will present the efficacy results, first, as related to treatment of obesity, and then in type 2 diabetes.

Finally, I will present our understanding of the relationship between the metabolic improvement and the body weight loss.

[Slide.]

The epidemic of obesity is a major public health concern in the United States. It is estimated that over 30 percent of the people in the U.S. are obese and that over 60 percent of the total population is overweight or obese.

[Slide.]

In parallel to the epidemic of obesity, an increase in type 2 diabetes is also observed. Over 20 million U.S. citizens are diabetics and, in fact, type 2 diabetes and obesity are closely associated.

As shown, in a man with a BMI above 35, the related risk of diabetes compared to normal BMI is 42, and up to 93 for a woman.

[Slide.]

What is the perspective of the obese patient? First, obesity can be a painful condition on a daily basis. The quality of life of the obese patient is impaired due to social discrimination, restricted activity, low self esteem, and social isolation.

Second, obese patients are frequently suffering from comorbidities that are due to or aggravated by their obesities, such as sleep apnea or osteoarthritis, back pain, and infertility.

Finally, many obese patients are suffering from dyslipidemia, or cardiovascular disease, or are concerned about the risk of developing such

comorbidities.

[Slide.]

In reaction, many patients are trying to lose weight, but, unfortunately, most weight loss intervention fails. One reason for these failures is the unrealistic weight loss goals that patients set for themselves as shown by the investigation on the right.

Patients with an average body weight of 218 pounds dream of losing 38 percent of their body weight and would consider 17 percent loss, representing 38 pounds, as a disappointment.

Frustration and disappointment lead many of these patients to products not approved for weight loss. Of \$1 billion spent annually on weight loss, 90 percent is for dietary and herbal supplements. Only 10 percent is for FDA-approved prescription drugs.

Bariatric surgery may be looked as a last resort. It is effective, yet carries risk and complications.

[Slide.]

Moving from surgery, what is the medical perspective? The goals for the medical treatment of obesity are more realistic than some of the patient expectations.

It has been demonstrated that a modest body weight loss of 5 to 10 percent is associated with significant improvement in key cardiovascular risk factors.

Moreover, this range of body weight loss of 5 to 10 percent also improves several comorbidities including sleep apnea, osteoarthritis, and also has a significant impact and beneficial on the quality of life of the obese patient.

[Slide.]

In addition, weight loss can prevent the development of type 2 diabetes. As is shown here from Diabetes Prevention Program study demonstrates that change in lifestyle that results in a 4 to 7 percent weight loss decrease the full year accumulative incidence of diabetes by 58 percent in overweight or obese patients with impaired glucose

intolerance that is pre-diabetes.

What are the therapeutic options?

The NIH guidelines for treatment of obesity is based on BMI and the presence of comorbidities, such as diabetes and hypertension. The guidelines state diet, physical activity, and behavioral therapy is the first-line therapy. Pharmacotherapy is to be started from BMI of 27 with comorbidity and in all patients from a BMI of 30.

Surgery is to be considered from a BMI of 35. The guidelines also state that since obesity is a chronic disease, short-term therapy is not useful. Rather, long-term therapy is needed always in conjunction with diet and physical activity.

[Slide.]f

What are the choices of FDA-approved drugs for the treatment of obesity? In addition to phentermine and other amphetamines approved in the '60s, which are still used today, physicians can prescribe either sibutramine or orlistat, the later being recently approved as OTC for the lower dosage

form.

[Slide.]

To sum up, obesity and type 2 diabetes is a growing epidemic.

Many patients use unapproved weight loss products and resort to bariatric surgery, effective but with risk and complications.

Modest 5 to 10 percent weight loss provides important medical benefits.

Pharmacotherapy is a recognized treatment from a BMI of 27 with comorbidities and from a BMI of 30.

[Slide.]

Moving now to the clinical development of rimonabant, I will start with the efficacy data supporting our proposed indication for the treatment of obesity.

[Slide.]

This shows the first pharmacodynamic study performed in humans. Twenty overweight patients were treated for one week with rimonabant 20 mg and placebo using a crossover design in a Phase I

Center.

As shown on the panel, they lost 1.5 pounds during this week of treatment on rimonabant over the placebo effect. In conjunction, there was a decrease in hunger as shown here, as well as a decrease in caloric intake as shown on the right.

[Slide.]

The next step was Phase II. A dose-ranging study was performed in 60 to 70 patients per group with 3 doses: 5, 10 and 20 mg compared to a placebo given for 16 weeks. All doses were significantly better than placebo and body weight loss and were well tolerated.

The effect of 5 and 10 mg were very similar, around 5 to 6 pound, as you can see on the slide, and 20 mg induces the greatest weight loss of 8.4 pounds as shown here.

Based on these results, the Phase III clinical program was designed with two doses, 5 and 20 mg.

[Slide.]

The Phase III RIO program, RIO meaning

rimonabant in obesity, comprised 4 pivotal studies conducted in over 6,600 patients, two, 2-year studies, RIO-North American and RIO-Europe, and two, 1-year studies, RIO-lipid and RIO- diabetes.

[Slide.]

RIO-North America and RIO-Europe were conducted in obese and overweight patients with comorbidities excluding diabetes. RIO-lipid included obese or overweight patients with untreated dyslipidemia excluding also diabetes.

RIO-diabetes was conducted in obese or overweight type 2 diabetes patients, not well controlled by metformin, also sulfonylurea.

The design of the 4 RIO studies was very consistent. The 4 RIO studies were randomized parallel, double-blind, placebo-controlled studies evaluating rimonabant 5 and 20 mg.

After screening, patients were prescribed a mild hypocaloric diet and exercise. These recommendations were continued throughout the study.

The placebo run-in period of 4 weeks

preceded the randomizations. As I said, both RIO-lipids and RIO-diabetes were one-year trials.

[Slide.]

RIO-Europe, now shown, had a duration of 2 years.

[Slide.]

RIO-North America had also a duration of 2 years, but with re-randomization scheme after the first year of treatment when the patients on Active were re-randomized either to stay on their active treatment or switch to placebo.

[Slide.]

The baseline demographics are presented in this table. The patients were in their mid-40s in all studies except in RIO-diabetes where they were in their mid-50s.

Most of the patients were females in RIO-North America and RIO-Europe, but the gender ratio was more balanced in RIO-lipids and RIO-diabetes.

The weight range varied from 208 to 230 pounds. The BMI was high across all studies

particularly in RIO-North America. All together, these 5 contained over 1,300 patients with BMI over 40.

The elevated weight circumference, high prevalence of abdominal obesity and, as expected, there was a high rate of co-morbidities as seen on the next slide.

[Slide.]

This shows the baseline cardiovascular and metabolic risk factor of the RIO Population. The most frequent metabolic abnormality was dyslipidemia, either high triglycerides or lower HDL cholesterol or high LDL, or a combination of these.

In RIO-lipids, dyslipidemia was presented in 100 percent of the patients and not treated per protocol.

In RIO-diabetes, more than 60 percent of the patients were dyslipidemic, were on a drug and generally a statin. By protocol, all patients of RIO-diabetes were diabetes. The pre-diabetic patients shown here represented a quarter of the

population of the three other studies.

Hypertension was present in 30 to 60 percent of the population and was frequently treated as shown here.

At total, 90 percent of the RIO population qualified for the trial had at least one co-morbidity. Thus, the population of the RIO trial was an at-risk obese population.

The completer rates were those expected in long-term studies in obese patients with overall no difference between the rimonabant 20 mg and the placebo group. More patients discontinued the study for subject request in the placebo group, possibly because their expectation of weight loss were not met, as just discussed.

More patients discontinue rimonabant 20 mg for adverse events, and this will be further discussed in the safety presentation.

[Slide.]

The results of the 4 RIO studies are shown the same way on this slide and on the next one.

The top part represent the

placebo-adjusted results using the ITT:LOCF approach, which was the primary analysis of all trials. At one year the placebo adjusted weight loss was rimonabant 20 mg was 10.5 pounds and was identical in RIO-North America and RIO-Europe presented here.

[Slide.]

Coming to the curves which represent the observed case, the time course and extent of body weight loss was very similar in the two studies, leading to a body weight loss for the completers of 19 pounds after one year of treatment with rimonabant 20 mg.

In addition to these 19 pounds, can consider adding the 4 to 5 pounds lost during the run-in period that I just point out, thus reaching close to 25 pounds at total as a mean body weight loss for the completer during the whole procedure.

RIO-lipids show now nearly identical results with a placebo-adjusted weight loss of 12 pounds in the primary ITT:LOCF analysis. It is notoriously difficult to achieve any significant

weight loss in type 2 diabetes patients.

It may have to do with less exercise, concomitant antidiabetic treatment that puts on weight or other mechanisms. It is therefore not surprising that the weight loss with rimonabant in this population is somewhat less than in the non-diabetic population, but still reaching 8.6 pounds in the ITT:LOCF and to adjusted data, and 13.5 pounds from baseline for completers.

[Slide.]

Here we see the placebo-adjusted weight and waist loss of the 4 RIO studies, and these highlight the consistency of the efficacy of rimonabant 20 mg and weight and waist loss across the study.

The results on the waist to conference parallel the results of the weight loss and points out the benefits of rimonabant for the treatment of abdominal obesity.

As for guidelines for treatment of obesity, another important analysis was to look at the rate of patients who have a good response of 5

or 10 percent weight loss or more of their baseline weight.

At both thresholds, the respondent rate was significantly higher with rimonabant 20 mg compared to placebo in all studies. The 5 percent threshold data are presented in the briefing package.

The 10 percent responders presented.

[Slide.]

As we saw in the three non-diabetic population, RIO-North American, RIO-Europe and RIO-lipids, rimonabant 20 mg tripled the effect of diet and exercise alone.

For reasons already outlined, the rate of responders in diabetes population are lower, but still there was an 8-fold increase in the respond rate with rimonabant compared to placebo as shown here.

[Slide.]

Let's now move to the metabolic effects of rimonabant. As we saw in the baseline characteristics, low HDL and elevated TG is a

frequent finding in obese and overweight patients.

Here are the results of RIO-lipid, the study with untreated dyslipidemic patients.

As shown on the top left, using the ITT-LOCF, there was an increase in HDL of 8 percent over placebo and here, on the observed case of 23 percent over baseline in the completers.

On the right panel, rimonabant 20 mg induced a reduction of triglycerides of 12 percent over placebo in the ITT-LOCF analogies and of 15 percent reduction versus baseline in the completer population.

[Slide.]

Here we see again the consistency of the effect of rimonabant 20 mg represented as placebo adjusted data across the four RIO studies. HDL rate by 8 percent across the four studies, triglycerides decreased from 12 to 16 percent across the four studies.

Non-HDL cholesterol decreased by 2 to 4 percent across the four studies and there was no effect on the LDL cholesterol as shown here.

These results were observed in a consistent manner in patients with or without diabetes and in patients with or without treated dyslipidemia.

[Slide.]

The durability of the efficacy of rimonabant was an important objective of the RIO program. This is why RIO- Europe and RIO-North America were designed as two-year trials.

In RIO-Europe, patients maintained a weight loss at 2 years of 9.3 pounds adjusted to placebo and 16 pounds compared to baseline.

[Slide.]

The durability of the effect was replicated in the RIO-North America study. In this particular study, I remind you that patients on active treatment were re-randomized after one year either to stay on their rimonabant treatment or to be switched to placebo for the second year.

As you saw in RIO-Europe, the patients who stayed on rimonabant for 20 mg maintained their initial weight loss up to 2 years. When patients

on active were switched to placebo, they progressively regained body weight without reaching their baseline body weight after one year on placebo.

This was an expected finding, this was expected.

[Slide.]

As with any chronic disease, when treatment is stopped, the disease reappears. When rimonabant was stopped, patients started to regain body weight.

[Slide.]

Let's now move to the efficacy data supporting our second proposed indication of glycemic control in type 2 diabetes.

RIO-diabetes studied two important groups of diabetics, though still not able to achieve adequate control when treated by metformin or by sulfonylurea as monotherapy.

SERENADE was conducted in a different diabetic population--that is, the treatment-naive patients. The design of the two studies shown here

were different. RIO-Diabetes was a 1-year trial with a placebo run-in, as you heard, and 2 doses of rimonabant versus placebo.

SERENADE was a 6-month trial without run-in and looking at rimonabant 20 mg versus placebo.

The baseline demographics of the diabetic patients are quite similar across studies. Patients in their mid-50s, race, gender ratio, body weight and BMI are the same. A1C was higher in SERENADE, but there was a run-in in Rio- diabetes where patients lost a little bit of A1C.

[Slide.]

Finally, as expected, for a treatment-naive population, the time since diabetes diagnosis was shorter in SERENADE.

RIO-Diabetes studied patients not well controlled by metformin, also sulfonylurea. The A1C change over time is shown here in the central panel. The effect of lifestyle changes were transient in the placebo and in the 5 mg group. Yet, there was a continuous decrease in A1C,

reaching 0.7 percent decrease in the ITT-LOCF on placebo adjusted data.

This improvement is confirmed by a reduction of the fasting glucose as shown on the right. At the same time, weight decreased as shown on the left. This is contrary to what is usually seen when, for example, sulfonylurea or glitazone is added to metformin. Therefore rimonabant is an oral diabetic therapy that has achieved significant glycemic control while also controlling or reducing weight.

Patients including the RIO-diabetes trial were stratified according to the background therapy, making this study as a type 2 studies in 1. Those will present a large sample of patients which could have been studied in two different studies. Here, the advantage is that patients in both strata were studied under the very same conditions. The same improvements were seen in both strata, for A1C and for weight loss.

[Slide.]

Rimonabant was equally and significantly

effective in both situations. SERENADE studied patients not previously on drug. There was continuously a decrease of 0.5 percent over placebo after 6 months of treatment. This improved glucose control is confirmed by a parallel reduction of the fasting glucose.

At the same time, weight decreased by 15 pounds versus baseline, and by 8 pounds over placebo. Thus, rimonabant is a oral antidiabetic has achieved significant glycemic control in treatment-naïve patients while also reducing weight.

[Slide.]

As you heard from Dr. Mackie, rimonabant increases adiponectin in vitro production by adipocytes. During the SERENADE study, and that is shown here, adiponectin increased significantly in type 2 diabetes patients on rimonabant as compared to placebo. This increase in adiponectin is an interesting finding in light of its recognized antidiabetic and antiandrogenic properties.

[Slide.]

Let's now move to the analysis of the relationship between the metabolic improvement and the body weight loss.

From a patient and a physician perspective, the nature of this relationship may be not a critical matter since it is benefit of the treatment that matters and not whether it is fully explained by weight loss alone or not.

[Slide.]

We use the linear regression methodology to explore the relationship between metabolic effect and body weight loss. This was an exploratory prespecified method in the statistical analysis plan. Let me first explain the model.

The relationship of a given metabolic parameter with weight loss in the placebo group is estimated using linear regression. If the metabolic effect is fully explained by the weight loss, then, the same relationship will hold in the active group and the placebo group, and the two regression line would be a line as shown now.

Then, whatever treatment group, placebo or

active, a given weight loss respond to a single given improvement in HDL. Otherwise, as shown now on the right, the two regression lines are no more aligned but parallel. Then, the difference is an indication that the effect could not be fully explained by the weight loss alone.

[Slide.]

Let's now consider the linear regression model applied to HDL cholesterol in any of the RIO trials.

As shown on the left, since the regression lines for HDL are parallel, the improvement in HDL for the same weight loss is better on rimonabant as compared to placebo. For A1C represented on the right, the two regression lines are also different.

Thus, for the same weight loss improvement in A1C is better on rimonabant as compared to placebo.

[Slide.]

Before concluding, I would like to share with you the results of the quality of life in the RIO trial. We used two instruments. In the SF-36 scale, the physical function improved on the

rimonabant while the score of the mental has decreased, which was explained by the subgroup of patients with mood disorders.

[Slide.]

We also used an obesity-specific validated instrument called IWQOL-Lite. This covered the domain of physical function, self-esteem, sexual life, public distress and work. Patients on rimonabant 20 mg reported significantly greater improvement in all domains of quality of life compared to patients on placebo.

[Slide.]

Finally, what is the appropriate patient in the view of the benefits of rimonabant?

It is adult patients ready to comply with diet and exercise, committed to a long-term treatment with a base or overweight with 1 or more of the following risk factors: hypertension, abdominal obesity, or dyslipidemia; or, who is an overweight or obese type 2 diabetes not well controlled by metformin or sulfonylurea, who is at risk to gain weight to attain some improvement in

his glucose control.

[Slide.]

It is now time to sum up. Rimonabant 20 mg induced a significant reduction in weight and waist, as well as a significant improvement in HDL cholesterol and triglyceride levels. These effects were maintained up to 2 years of treatment.

Rimonabant 20 mg significantly improved A1C and body weight in type 2 diabetes with different background therapies and in treatment-naïve patients.

The metabolic improvement cannot be fully explained by body weight loss alone. With the obesity specific quality of life measurement tool, all domains of quality of life were significantly improved.

Importantly, the efficacy data were consistent in 5 clinical trials. Thus, the data support the proposed indication of rimonabant in the treatment of obesity and improvement of glucose control in type 2 diabetes.

I thank you for your attention.

DR. GURAL: Thank you, Dr. Rosenzweig.

I would now like to introduce Dr. Paul Chew, who is the Vice President for Metabolism, Diabetes and Thrombosis in Clinical Development for Sanofi-Aventis.

Dr. Chew.

Clinical Safety of Rimonabant

DR. CHEW: Thank you, Dr. Gural.

Good morning, Mr. Chairman, members of the Committee, ladies and gentlemen.

I am here this morning to present to you the safety experience with rimonabant in the clinical program. My name is Paul Chew and I head the Clinical Development for Metabolism, Diabetes and Thrombosis at Sanofi-Aventis.

[Slide.]

This presentation will focus on the Phase III program and specifically the obesity and type 2 diabetes programs as these are the requested indications.

Given our limited time, I will refer the Committee to the briefing book for data from the

Phase I and Phase II studies. We will begin the overall safety profile of rimonabant and then follow with a special focus on adverse events of interest including data from the completed and ongoing trials.

[Slide.]

These figures were reviewed earlier by Dr. Gural, so I will summarize them here.

We have over 15,000 individuals exposed to rimonabant as of March with 1190 in Phase I and 1008 in Phase II.

The Phase II program was conducted in various populations including obesity, smoking cessation, prevention of alcohol relapse and in schizophrenia. The far greater part of the exposure has been in Phase III where almost 13,000 patients have been enrolled with 7,447 with 20 mg from 1 day to 2 years at 20 mg. We have 3,478 patient years.

[Slide.]

During the conduct of Phase III, adverse events were routinely collected via open

questioning. The safety analysis followed guidelines from the International Conference on Harmonization, a project that achieves greater harmonization in the interpretation and application of technical guidelines and requirements for product registration.

Safety analyses were performed in these pools. Today's discussion will focus on the obesity and diabetes indications, and we will include the other population for very rare events, such as seizures or suicidality.

[Slide.]

The number of patients exposed for completed Phase III studies for an obesity and diabetes is shown here. Please note that RIO-diabetes was conducted as part of the obesity program. But SERENADE, its companion study, was analyzed also with the diabetes population.

As a cue in the future slides, you will see 2474 under the placebo group as a grouping for these 7 studies and 488 as a cue for the type 2 diabetes studies.

To obtain the most complete and transparent accounting of patient exposure, the sponsor counted patient exposure based on the treatment received.

For RIO-North America, as Dr. Rosenzweig had indicated, there was a re-randomization from 20 mg to placebo or maintaining 20 mg with the beginning of the second year. The same with 5 mg as well.

So, we retained the exposure after treatment received. So, patients who were on 20 mg for 2 years counted for the 20 mg exposure. Those who were randomized to a placebo on the second year were counted on the first year and 20 mg second year on placebo.

Moreover, our analyses comprised the 7 studies. These accounting conventions differ from FDA where the safety analysis included only the 4 RIO studies and moreover, re-randomized patients were not counted in the second year if they had been re-randomized downward.

The re-randomized patients who were

maintained in their analysis were those who maintained the same dose throughout and, if they were re-randomized downward, only the first year was kept.

It is important to articulate these differences now, so that you will be able to understand better the subsequent analyses I will present.

[Slide.]

This is the smoking program which will not be discussed today. But here are the total exposure listed here again in patients exposed.

[Slide.]

As of March 1st, there were 11 ongoing clinical studies with 14,280 additional patients included. Of course, these studies are blinded, but with a 1 to 1 randomization to 20 mg or placebo. This provides approximately 7,855 patient years.

As discussed earlier by Dr. Gural in the introduction, these ongoing clinical studies are focusing on patients at increased risk for

cardiovascular outcomes.

[Slide.]

We will first review the overall safety profile in obese and diabetes and the events that led to premature discontinuation.

Adverse events were collected, as I said, by investigators in an open questioning fashion at each visit, and by "open questioning," I mean a non-directed approach. Specifically, in light of the presentation by Dr. Posner, suicidality was not prospectively obtained. But I will say more on this later.

[Slide.]

Shown here are the common adverse events in the obesity studies occurring in at least 2 percent of rimonabant-treated patients and more than 1 percent over placebo.

They were GI, nervous system and psychiatric disorders. The most common GI event was nausea, occurring in 13.6 percent versus 4.7 percent, with a difference of about 9 percent between the groups, compared with approximately a 2

percent difference with diarrhea and vomiting.

For nervous system disorders, dizziness was the most common, with approximately a 3.2 percent difference between the groups.

For psychiatric disorders shown here, anxiety was 5.9 versus 2.1, and, with insomnia, mood alterations, and depressive disorders as shown.

[Slide.]

In the diabetes population, the events were similar overall, as you can see, however, there were events of hypoglycemia and muscle spasms that were more associated with the diabetes population and, relative to the obesity population, there was a somewhat greater incidence of paresthesias.

Almost all of the hypoglycemic episodes occurred in the RIO-diabetes program, a trial with background sulfonylurea or metformin and, in that study, hypoglycemia was reported with both background therapies.

In SERENADE, a study with the

treatment-naïve diabetics with no background therapy, there were two cases of mild symptomatic hypoglycemia, one with rimonabant, one with placebo.

[Slide.]

So, in the obesity program, adverse events were mostly of GI, neurologic and psychiatric origin. They were of a similar nature in the diabetes population with additional events, such as hypoglycemia, muscle spasms and paresthesias.

[Slide.]

In the obesity and diabetes programs, deaths were few and balanced across the doses - 3, 3, and 4, as you can see.

The same was the case with diabetes. Ongoing clinical trials have recruited more than 14,000 patients at risk for cardiovascular outcomes and are being monitored by an independent data and monitoring committee.

[Slide.]

We will move on to an in-depth review of the adverse events of interest.

[Slide.]

Rimonabant acts both centrally and peripherally. Adverse events of interest were psychiatric and neurologic events, as shown.

Because of their medical importance, we examined suicidality and depressive disorders. In addition, we will also discuss anxiety, which was reported in the clinical studies.

Finally, we will review the neurologic adverse events with special attention to multiple sclerosis and seizures.

[Slide.]

With the advice of FDA and the Swedish health authorities, the specific methodology was implemented prospectively during the course of the RIO studies to specifically monitor depressive events.

Any symptom possibly attributed to the depression by the investigator triggered a psychiatric consultation to better assess the diagnosis using DSM-IV criteria

But to increase the sensitivity in

addition to the spontaneous open questioning from investigators, a patient self-assessed scale, the Hospital Anxiety and Depression Scale was completed regularly during the 7 obesity studies to help the investigator to identify undetected cases when the depression subscore of that scale reached 11 or greater and, it is important to note that, on that scale, there was no question for suicidality.

In a retrospective assessment we went back with cooperation from the sites and on recommendation of the FDA, we went back to all cases of neuropsychiatric events to the site and to all patients who received antidepressant therapy, or who had severe anxiety or other psychiatric disorders.

All these cases were fully documented to a specific questionnaire, focusing at the site level on outcome and associated symptoms including suicide attempt and ideation in this retrospective assessment and through collection of source documentation including medical reports and investigator notes.

Finally, and this is important, if a patient during the course of the studies required antidepressant therapy in the RIO program, he or she was automatically discontinued from the study treatment to avoid the confounding effects of the therapy on body weight loss.

[Slide.]

Under the MedRA safety classification, the high level group term depressed mood disorders and disturbances is shown here, 4.5, 8.4 percent, approximately a 4 percent difference.

This breaks down into two subclassifications which may look very similar in terms of the wording, and there is approximately a 2 percent difference there. But they do have different clinical earmarks.

[Slide.]

The medical history part of the case report form sometimes had written in a past history of depressive disorders from the site.

On the left, you can see that the rimonabant and placebo treated patients with mood

alterations were very similar more or less, with a past history of depressive disorders recorded in the case report form of about 15 percent, a quarter needed to stop the treatment whether it was placebo or rimonabant.

The corrective therapy was about a third of patients--two-thirds did not require it--and the median time to recovery was very similar between the groups when there was therapy or not, and there were no hospitalizations.

So, there is really no distinguishing earmarks on the rimonabant and placebo site there.

Similarly, for patients who had depressive disorders, these were very similar, 40 percent past medical history of depressive disorders, about 60 percent discontinued. Corrective therapy, usually antidepressant therapy in over 70 percent.

Given the small numbers it is hard to really say because we have the small numbers on this side. There were hospitalizations, somewhat more observed here, but it was 1 out of 43, 4 out of 106 compared to the mood alterations.

So, this group is similar to itself, this group is similar to itself. The difference is when you go across the line. Patients with depressive disorders more often had a history of past depressive disorders. They more often had discontinuation, need for corrective therapy, and there were occasional hospitalizations.

So, mood alterations with depressive symptoms are not the same at all as depressive disorders.

[Slide.]

Now, I am going to look at it the other way around. In the previous slide, we saw that given mood alterations of depressive disorders, a past history of depressive disorders was more frequent in the latter group.

A feature that was the case with both placebo, as well as rimonabant-treated patients, each side was similar to itself in terms of rimonabant and placebo.

In this slide, we look at the situation the other way around. Given a past history, was

there a greater likelihood to develop these disorders in the study.

On the left, in patients with no past history of depressive disorders, which of course is the majority of the database, the numbers look very similar to the overall safety profile I showed a few slides back.

In spite of 2 percent difference here, 1 percent, 2 percent here, I am highlighting this line because I want to keep your eye on it.

In the patients with a past history, which are here, fewer, what you can see is that mood alterations with depressive disorder is doubled if you had a past history and so did the rimonabant.

Skip the yellow line. Anxiety doubled. Everything doubled when you were on the side with a past history. The yellow line is different. You went up 8- to 9-fold. On the placebo side, if you had a past history, you were more likely to have a depressive disorder on the placebo side.

On the rimonabant side, same thing, about 9-fold. So, whereas a past history tended to raise

all boats about 2-fold for these, with depressive disorders, there was an amplification of about 9-fold for both placebo and rimonabant equally.

So, a past history predicted a future event more often, in general.

[Slide.]

So, in summary, depressive-related events were reported by investigators more often with rimonabant and, among these adverse events, we can identify two different types. The mood disorders that generally recovered without the need for corrective therapy or discontinuation, and another category of depressive disorders which required more frequently corrective treatment and hospitalizations and there was a consistent but modest difference between the placebo and the rimonabant groups.

Now, as seen in other studies, patients with a past history of depressive disorders are at a risk of another event, a fact that was as true for placebo in these studies as for rimonabant.

Therefore, in considering who is the right

patient for rimonabant from a safety point of view, we will recommend not treating patients with a history of depression or suicidality, not treating patients with an active diagnosis of depressive disorders or current antidepressant therapy.

This is the overall difference in the original table of adverse events. If we were to exclude past history of depression, you see you go from 3.9 and 1.7. You can see the 2.2 percent difference, and you can see it is much more now, it is about 1.3 if you exclude the past history alone.

[Slide.]

In patients with depression as we heard this morning from Dr. Posner, the most serious concern is the possibility of suicide. The following slides are related to suicidality, which refers to any suicidal thinking or behavior. You have heard a lot of this already, so I will go through it a little faster.

[Slide.]

Working with FDA, as I said, the sponsor went back to the sites, requested source level

information on more than 4,000 patients who had neuropsychiatric events in the RIO and the STRATUS smoking program. We summarized this information in blinded anonymized narratives of the events, prepared from over 22 studies, completed clinical studies for evaluation by C-CASE.

These included the Phase II studies, as well as the methodology calling for all completed studies, that were double-blind, randomized, clinical studies with more than 20 patients per group.

The results of this retrospective data collection was developed with an analysis and methodology by Dr. Posner and her colleagues as she discussed this morning, and it is now a standardized approach recommended by FDA based on the previous experience with the antidepressants.

[Slide.]

I won't go through the scale, which is shown here, other than to say there were groupings as part of the subsequent analysis, which was definite suicidality, which was 1, 2, 3, or 4. So

that was grouped as a definitely suicidal behavior or activity. And then we had 5, 6, and 9, as Dr. Posner indicated as possible. 7 and 8 were considered neither definitely nor possibly suicidal.

Because of the rarity of these events, all Phase II and all Phase III studies were included, including alcoholism, schizophrenia, and, based on a classification across these studies, whether it was smoking, diabetes, or obesity.

And 88 cases under placebo or rimonabant were identified. Twenty were in the Phase II schizophrenia and alcoholism studies, certainly a more vulnerable population, and suicidality cases were identified retrospectively from source documentation. Sometimes there was no exact time of occurrence recorded.

So, all cases were attributed to the first randomized treatment, whatever the randomization was at that moment. So, if a patient had been re-randomized downward to a placebo or a lower dose, we attributed the event to the original

higher dose.

[Slide.]

The results are shown here. These are the numbers here for placebo, rimonabant, rimonabant, for categories 1 through 4, definitely suicidal, possibly suicidal, 21 cases, 11, 48.

This is the tabulation of the data as we collected it using the method I just spoke of. This way of considering all the studies differs from the FDA where meta-analytic techniques were used to adjust for the structure of individual studies.

Using that approach, FDA used 5 mg as a placebo for studies without a placebo arm. It was a stand-in for placebo. Using that approach, STRATUS-worldwide, which was a large study of 5,000 patients in smoking, the 5 mg arm was used in their analysis as a placebo when compared to the 20 mg arm in that study.

As Dr. Rosenzweig has shown, the 5 mg dose is active with statistically significant weight loss. For that reason it is an active dose, not a

placebo dose. If FDA is to consider for some safety analysis that 5 mg is a placebo or inactive, then, for clarity and consistency, it should consider all events on 5 mg as the equivalent of placebo events.

Clinical data and pharmacology show us that 5 mg is active and therefore, the sponsor has considered 5 mg as an active case and classified the events accordingly.

Although this can be explained further in the discussion period, we will consider the suicidal ideation data for the obesity and diabetes shown on the next slide.

[Slide.]

In the completed Phase II and Phase III studies for obesity, for the completed studies there was 1 case of suicide attempt. By the C-CASA analysis, there was no classification 1 of completed suicide.

What we wanted to look at here is the suicidal ideation 0.36, 0.62, approximately a 2-fold imbalance that we see for suicidal ideation

in the obesity and diabetes studies. Under the possible suicidal events, they are much less frequent and there does not appear to be a signal there.

The important point to make is that among the cases of suicidal ideation reported in the obesity studies, as shown here, 100 percent, all of these cases were associated with a concomitant depressive disorder or adjustment disorder as Dr. Posner has indicated today.

These did not occur as isolated events. Moreover, in addition to the concurrent illness, half of them, 50 percent, had a past history of depressive disorders. And that was true for placebo. It was true for rimonabant. And most had significant life stressors at the time.

These patients recovered with corrective treatment of the associated depressive events, 3 patients were hospitalized, 1 on placebo, 2 on rimonabant 20 mg for depression and major depressive disorder.

[Slide.]

Now, in addition to the previous analysis we just showed, we performed a supplemental meta-analysis which contrasts with the FDA's analysis. We used a meta-analysis technique using the so-called Peto method. The Peto method, looking at the overall database, yielded an odds ratio of 1.3, which crossed below 1, and went up to 2.3. This is in contrast to the overall assessment of 1.9 with the lower limit of 1.1 and up to 3.

Why the difference from the FDA analysis, why 1.9, why 1.3? The estimates of the two special population studies, schizophrenia and alcohol, in obese patients, here 1.8, 1.6, and the special populations 1.4 and 1.1, are largely consistent with this analysis between the two approaches.

Where the analysis differs is in this smoking cessation line. Again, this is due to the handling of 1 placebo-controlled study, the STRATUS worldwide study.

This was a study in patients motivated to quit smoking. Patients were randomized either to 5 mg or 20 mg for a period of 10 weeks and a quit

phase during the first two weeks. Those who were abstinent at the end of 10-week period were re-randomized in a similar fashion to RIO-North America. Any event that occurred afterwards was always attributed to the previous higher dose.

In order to adjust for that study structure where there was no placebo control, FDA used the 5 mg as the placebo control, which we do not feel is appropriate for several reasons.

First, as there were other rare events which occurred in the 5 mg group, either less frequently or not at all in the 20 mg group, this introduces inconsistent handling of the 5 mg group data as we move from one analysis to the other. When is the 5 mg a placebo and when is it an active dose?

The sponsor took an approach of using placebo-controlled studies only where a placebo is always a placebo.

Secondly, the incidence rate of suicidality for the 20 mg group in the uncontrolled STRATUS-worldwide study for the 20 mg was about

0.40 percent, very similar to other studies in the STRATUS program, so that treatment arm did not influence much the overall estimate for the 20 mg group whether including or excluding the 20 mg.

However, because of the unusual zero event rate in over 2,000 patients in the 5 mg group, deeming it as a placebo controlled as the FDA did, significantly dilutes the estimate of the placebo rate, substantially.

Therefore, the sponsor conducted the meta-analysis without this study using only placebo-controlled studies, using the Peto method, and yielding the overall estimate of 1.3 with a confidence interval which shows that the overall odds ratio for suicidality is not significantly different from 1.

[Slide.]

This table shows our current experience with rimonabant. In the completed clinical trials, it was the one case on the C-CASA table where it was felt not to be sufficient data for classification as a confirmed suicide, the

investigator reported it as a suicide, we are counting that as an investigator reported suicide.

This is the most current exposure in patient years and, in the completed trials, the event rate per 100,000 patient years is 14. And, for patients with a BMI over 30, in the U.S., the base rate is expected to be about 13. So, we have 14 in the completed clinical trials.

As of May 2007, two reported cases of suicide in the ongoing clinical trials and 1 postmarket case of suicide was reported. This one is via secondhand information and the patient allegedly receiving rimonabant. The data are very, very unclear at this point.

[Slide.]

I want to review briefly the narratives of these patients. This 36-year-old man was in the STRADIVARIUS study looking at atherosclerosis progression, had been exposed for 10 months, had a myocardial infarction one week prior to inclusion.

After 8 months, the patient who had no psychiatric history presented with a depressed

mood, irritability and fatigue. There were serious financial stressors at the time, depression worsened within 3 months with no corrective treatment and no psychiatrist or specialist was consulted.

CRESCENDO is the ongoing cardiovascular outcome trial, 77-year-old man. Again, this was received on May 22nd, very recently. Forty-five weeks into the exposure on rimonabant. He had a prior history, past history, of depression at age 40, and additional further episodes.

About 10 months after the study start, patient became depressed and he discontinued rimonabant on his own. He visited a psychiatrist who prescribed an SSRI but committed suicide one week later. The psychiatrist evaluation revealed depression, loss of energy and interest, marital difficulties, and the progressive worsening of neuropathy.

[Slide.]

In the third case, RIO-North America, 63-year-old man on 5 mg. Please remember that was

not the dose, 5 mg is the case here. Gunshot wound. Apparent suicide according to the investigator. Depressive symptoms and anxiety. At the last visit, however, there was no sign of despondency, hopelessness or outward signs that the patient was suicidal.

But from the nurse, it was found patient couldn't eat and had slept 30 hours, was found dead in front of his house. There was a past involvement in the Federal Witness Protection Program and he was pending a very important court decision according to the medical notes.

[Slide.]

For the ongoing studies, the Phase IIIb studies, C-CASA has evaluated the data from our ongoing studies as of May 29, 2007. Similar blinded review of clinical information was performed on 35 cases of potentially suicidal behavior or ideation.

There was an imbalance seen in the definitely suicidal classification of 1 through 4, of 0.30 versus 0.14 percent. Based on the

estimated--this is the estimated exposure because these trials are ongoing and double-blind.

As I said, the postmarketing case for which we have very little information, and the recent case in CRESCENDO are included here. But it is important to note that suicide attempt, the overt act with the intent to die, No. 2 here, there were two cases of suicide attempts in placebo with the intent to die, 2 suicides here in the rimonabant group, suicidal ideation, as with the obesity and diabetes study. The imbalance is about 2, 2.5 fold, 0.11, 0.28.

So, at the current time, based on the C-CASA analyses, the blinded analyses, there has been one suicide in the completed trials and in the ongoing trials it is 2 with 2 suicide attempts also noted on placebo.

We continue to closely monitor suicidality in the ongoing studies with a scripted psychiatric questionnaire including a search for suicidal ideation.

What I would like to inform the Advisory

Committee about today is that in the ongoing and future clinical trials of rimonabant, in order to better establish the extent and significance of suicidality, Sanofi-Aventis will be implementing the questionnaire discussed today by Dr. Posner and her colleagues.

We will be using that going forward. Basically, if you want to get the answer, you have to ask the question, and that is the lesson of the questionnaire. We will be using that.

[Slide.]

We have reviewed suicidality-related events and they are completed in the ongoing studies, as well as the postmarketing experience to date. It was an imbalance and definitely suicidal behavior and ideation in the obesity and diabetes studies, 0.65 versus 0.36 percent, driven largely by the differences in suicidal idea.

There was one suicide reported in the completed trials in a patient randomized to 5 mg at a rate consistent with the epidemiologic studies in that population, and the ongoing studies, a similar

picture emerges.

When there was an imbalance in suicidal ideation, but not behavior, with two completed suicides in rimonabant 20 mg, and two suicide attempts on placebo. It is important again to repeat suicidal ideation did not occur in isolation, on the contrary, it was always associated with other psychiatric disease, most often depressive disorders that were medically manageable.

Overall, the rates of suicidal ideation and behavior are low. You saw the epidemiologic figures this morning from Dr. Posner. Consequently, a causal relationship has not been established between suicidality and the use of rimonabant.

[Slide.]

Anxiety-related and panic disorders were also reported with anxiety 5.9 percent on rimonabant being more frequently reported than with placebo 2.1 percent, an incidence over placebo of about 3.8 percent.

Again, anxiety and panic disorders are not formal psychiatric diagnoses. These are based on verbatim statements of the investigators with classification and evaluation by the MedRA hierarchy.

[Slide.]

The main characteristics of the anxiety disorders and symptoms were comparable, past history of depressive disorders much less frequent.

Treatment discontinuations on the order of 15 to 20 percent, compared to the depressive disorders, which was about 70 percent.

Corrective therapy, usually anxiolytics in about 40 to 50 percent, very comparable times to recovery whether or not there was corrective therapy, and really no significant medically important cases. The one hospitalization was in a patient with a panic disorder, tachycardia, and diaphoresis and chest pain. It was a 3-day hospitalization.

[Slide.]

We performed an extensive review of the

neurologic symptoms, such as sensory changes, motor impairment and cognitive difficulties according to the categories agreed with FDA. This review includes reports of complementary consultations and investigations as part of that retrospective assessment.

Shown here for the obesity studies and also similarly for the diabetes studies, sensory changes were the most frequent, the higher frequency in rimonabant 20 mg as compared to placebo. Again, dizziness of approximately a 3, 3.5 percent difference.

A paresthesia on the order of half a percent difference. Again, the latter occurred more frequently in the diabetic patients. Two cases of paresthesias were actually transient ischemic attacks.

In the motor impairment category, there was really no event that met the 1 percent criteria difference, but tremor was close, so we put that up here. It is about 0.9 versus less than 0.1 percent.

In the rimonabant group, there was no serious case of tremor. It was not Parkinson's disease. It was not felt to be medically important or require hospitalization, and patients maintained rimonabant or placebo in about 80 percent of cases, or rimonabant for 80 percent of cases.

Cognitive difficulties are shown here, 4.1 versus 2.1, a 2 percent difference. It was most often reported as a short-term memory loss, memory impairment, or amnesia. No case was felt by the investigator to be medically important or require hospitalization.

Fifteen percent of patients discontinued rimonabant, most did not, and 12 percent discontinued with the placebo, so the discontinuation rates between rimonabant and placebo for memory loss were very similar.

[Slide.]

What about the neurologic adverse events that led to actual discontinuation of the therapy?

Discontinuations for neurologic events was infrequent, but there was an imbalance. Overall,

2.2 percent of patients discontinued rimonabant due to neurologic AEs compared to 0.6 percent on placebo group with the most common reason being dizziness. But it should be noted that dizziness was often reported in concurrence with GI symptoms, such as nausea.

[Slide.]

This table addresses the issue raised by FDA on the cases of multiple sclerosis. This table shows the incidence of new cases of multiple sclerosis occurring during the clinical trials. It is a little busy, but there was one placebo case, 2 at 5 mg, and none at 20 mg with a patient year exposure estimated there for the placebo, the event rate was 29. It was a very wide range, of course, given one event.

When you look at 5 mg and 20 mg, we consider those active doses. We had two cases at 5 mg, none at the proposed therapeutic dose. The event rate, again given a scant number of cases, is 29 with a very wide interval.

So, when you consider the one and the two,

there is no increase there. The FDA has questioned the multiple sclerosis diagnosis in the placebo case.

The sponsor consulted Dr. Dan Michael, a neurologist, to review this case. He has confirmed the diagnosis. Dr. Michael is here today and available to discuss his evaluation.

There was one case here. At the end of April postmarketing, it was not confirmed. There have been no cases of reconfirmed multiple sclerosis in postmarketing. But there was one case of bilateral papillitis, optic neuritis one month after starting rimonabant reported as a potential multiple sclerosis. But the MRI results are not available to the sponsor, and it was rated as suspected MS, multiple sclerosis by the reporter.

[Slide.]

In addition, there has been a case of a patient with existing multiple sclerosis who experienced vomiting and a gait disturbance 5 days after starting treatment. It is not a new case, it's a patient with multiple sclerosis who had a

gait disorder with vomiting a few days after starting rimonabant.

An MRI was obtained. There was no change from the previous MRI four years before, and the gait disturbance resolved within 3 days.

[Slide.]

In addition, the FDA has listed two potential cases of multiple sclerosis and I would like to briefly discuss them here.

In addition to the three confirmed cases that were discussed in the prior slide, there was one case of a patient evaluated for MS but who did not meet the diagnostic criteria. A 49-year-old woman evaluated for a balance disorder. The MRI scan was not consistent with MS. Updated information. We got information on this patient. It is 3 1/2 years later now. The patient has had no new events and has had normal annual examinations. This is not a case of MS.

In the second case, the patient had pre-existing MS diagnosed 5 years prior to entering the study. During the treatment period, the

relapses have been similar to those before the study and also after the study. This not a new case of MS.

[Slide.]

I will now move to the evaluation of seizures. In Phase II and Phase III, patients with treated epilepsy with anti-epileptic therapy were excluded. However, patients with a medical history of epilepsy or seizures, not currently treated, were allowed in.

Forty-eight patients of such a history were randomized in the trials. Because the cases of seizures were again rare, we analyzed all the databases for Phase I, Phase II, Phase III including vulnerable populations for seizures, such as schizophrenia and alcoholic patients in Phase II.

We took this approach in order to be comprehensive and not to miss any trials or any patients. For completed studies, we searched for all potential cases, not only those reported by the investigators as seizures and coded accordingly by

MedRA, but also cases evocative of seizures using a string search, which is very hard to read probably, convulse, petit mal, grand mal epilepsy tonic/clonic, and so forth.

So, this was a big search for seizures, ostensible and perhaps occult. All the identified cases were reviewed blindly by two neurologic experts who had access to all of the available source information and, in some questions, where they raised questions, we went back to the sites to get the information if it was available.

[Slide.]

FDA and the sponsor analyzed the seizures differently, and this is based on Table 31. FDA included only studies with a report of a seizure, of which there were 8. Cases that were excluded were those in the placebo run-in on the lead-in, and three months after the study end, the lead-out, if you will.

They included cases in non-placebo-controlled phases or studies, a similar theme to what I have said before with 2 cases and

20 mg, and the overall comparison was 20 mg versus placebo. The sponsor analysis is on the right, included all the completed studies without events.

It included all the reported seizures whatever the phase. I compared rimonabant all doses versus placebo. Two analyses were performed; all seizures, possible, likely or unlikely, and those that were felt likely or possible seizures as assessed by the external experts.

[Slide.]

This is the sponsor analysis. Nineteen cases were reviewed by the experts. Fourteen were assessed as likely or possible and the five were felt to be unlikely.

The number of events per patient year--this is an incidence rate now. These are the patient years right here, 3200 to 3600, all 19 cases, and you can see that the incidence rate is 0.23 for placebo, 0.2 for rimonabant 20, and 0.06, all doses culminating in 0.16. And when you take the confidence interval of all doses versus placebo, the relative risk is 0.68 straddling 1.

That is all cases.

Now, when you take the cases that were reviewed and felt likely or possible by the experts, we have 0.17. Two cases didn't make it in placebo. And we had 3 cases didn't make it in placebo in 20, it is 0.17, and the answer is the same. The risk ratio straddles 1. There was no increased risk in this very large database of the completed clinical studies.

[Slide.]

I would like to compare the FDA analysis on top with part of the table. I simplified the table but it is the same numbers as you saw before, excluding the two placebo run-in cases and the one late event and including 2 mg cases where we have no placebo, you see. We kept the active dose, no placebo. These are the numbers here, and then you have the 20 mg versus placebo at 1.69. But even with that analysis, you see the relative risk straddles 1.

[Slide.]

This is just a summary, just so you don't

have to go back, is the sponsor analysis, all studies, all cases, unlikely, possible likely, includes all reported cases. We showed them here.

This is the number you just saw. If we do the 20 mg versus placebo comparison instead of all doses, you get 1.08, again straddles 1.

So, no matter how you do it, you get a relative risk that is on both sides of 1.

[Slide.]

Ongoing studies. There have been 8 cases of possible seizures reported. All were blindly adjudicated by the same experts, the same system, and then unblinded. This is what it turned out.

Eight cases. There were four on 20 mg, two on placebo felt to be possible or likely, two were felt to be unlikely. That is the split. If you count them all, all the 20s is seizures, then, you get 0.15 percent. If you use the adjudication, the possible or likely, you get 0.1 percent, numbers that are very similar, similar to that observed in the completed studies.

This information is very, very important,

because we were alerted by toxicological preclinical data, which suggested early that we might have a problem.

During the Phase I studies, a little later, and a repeated dose study for 21 days, three weeks, up to 60 mg, three times the therapeutic dose, there were no seizures.

You supplement that clinical experience with the many analyses that have been done, the large clinical database, which we have in obese patients, is very reassuring. There is no increased risk of seizures that we have shown.

[Slide.]

Now, I would like to conclude with our assessment of overall safety and make some points with another agent, with a favorable benefit-risk profile.

The rimonabant development program has been, continues to be an extensive program. in addition to the more than 6900 patient years of exposure, the trials have shown a consistent safety profile with no new signals in the postmarketing

worldwide experience with more than 100,000 patients treated since the approval in Europe one year ago.

Rimonabant is well tolerated in obese and diabetic patients. We will focus, not on the GI, we will focus on the adverse events of special interest in patients, something that is of interest to them, of course, and their treating physicians.

I would like to frame this in a way to address the questions submitted by FDA on the sufficiency of the demonstrated safety profile.

First, depression. This was reported more often with rimonabant with a consistent but modest imbalance compared to placebo. Compared with a placebo, the need for corrective therapy, the time to recovery are very similar.

Second. Although there was an imbalance in suicidal ideation, this was always associated with a treatable depression or adjustment disorder, very consistent with a much larger experience that Dr. Posner and her colleagues had with this issue over all.

The report suicides, very rare in the completed clinical trials. Comparable to the expected background rates, because of the many reasons listed on the way we obtained this information, no causal link has been shown with the use of rimonabant.

Moreover, I will repeat now we will be using the questionnaire to prospectively assess suicidality in the ongoing and future clinical trials, the one proposed by Dr. Posner today.

The most frequent neurologic events were dizziness, paresthesias, hyposeizures, tremor and memory loss with no imbalance in the really important ones, which would be serious cases, or reasons for discontinuation.

Finally, with multiple analyses, there was no signal, no signal for an increased risk of seizures.

Treated patients with epilepsy were excluded from the Phase III studies. They are now allowed in these on-scoring studies because these studies are being monitored by an independent

external DMC, and we do have experience now on the risk of seizure. There is no risk of seizure that we have shown.

For the general population, however, we do not recommend patients who are currently being treated for epilepsy to be included.

[Slide.]

I would like to put into perspective the reported safety profile of rimonabant by briefly considering another agent. You heard briefly today about sibutramine. It's an approved agent for weight loss. This is relevant text from the package insert. It is very appropriate given our discussion today. This is the fragment I have taken out.

Cases of depression, suicidal ideation and suicide have been reported rarely in patients treated with sibutramine. However, the relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine.

If depression occurs during treatment

with sibutramine, further evaluation may be necessary.

Now, this fragment of the label may appear of concern, of course, especially without knowledge of the clinical utility. My point is that the safety of this drug or any drug can only be evaluated in light of the demonstrated benefits and the medical need that it attacks.

So, as I finish my presentation, I hope the Advisory Committee will agree with me that the sponsor, through a series of integrated and consistent trials in obesity, overweight and diabetes patients has identified the safety profile of rimonabant and the issues that will need monitoring and appropriate labeling.

To this point, that the safety profile can only be interpreted in light of the demonstrated benefits discussed by Dr. Rosenzweig for reducing weight, reducing cardiovascular risk in patients who are overweight and obese patients, as well as the highest risk patients, the highest risk patients with type 2 diabetes having diabetes is

the same as having had a heart attack in terms of future cardiovascular risk and that continues to be a growing and still challenging medical need.

[Slide.]

Finally, Mr. Chairman, members of the Committee, after one year of use in Europe and other countries worldwide, the postmarketing experience of rimonabant confirms the overall safety profile that has been defined in the submitted dossier.

Based on the data presented today, the sponsor has defined a safety profile that identifies the right patient, and more importantly, the wrong patient for rimonabant.

As Dr. Gural said moments ago, patients with a history of depression or suicidality, current depression, are receiving antidepressant therapy are not the right patients, and neither are patients at this time with treated epilepsy.

We have not had the time to discuss all the safety data and we will be available to the committee if there are further questions.

Thank you, Mr. Chairman.

DR. GURAL: Thank you, Dr. Chew.

I would now like to review with the Committee the risk management plan that Sanofi-Aventis is proposing.

[Slide.]

The risk map will take three main elements. First, it will focus on the identified risk. As we have heard this morning, there are three risks associated with the use of rimonabant - that of increased risk in patients with depression, potential risk in patients receiving antiepileptic therapy and, lastly, the short-term use.

[Slide.]

We will also discuss today some intervention tools for the reduction of these risks and the minimization, and, lastly, we will discuss how we will assess the effectiveness of those tools.

[Slide.]

First, as we identified this morning and throughout the course of the discussion, three

primary risks have been associated or identified with rimonabant as indicated in this slide.

[Slide.]

We are recommending a number of approaches or interventions directed not only at the health care provider, but also at the patient and the family.

These are not only in terms of the routine measures, which will include for the health care professionals, continuing medical education, product focus education and an awareness campaign.

There will also be enhanced measures. A tool which we are going to call the physician's check list, which I will describe to you in just a few moments, a medication guide according to the CFR and agreement with the FDA.

An early patient access program, which we will describe and, lastly, something that we are calling now a physician-patient treatment plan, again bringing the patient and the physician together on the treatment of the disease.

For the patient and the family, there will

also be the routine measures; that is, we will provide education. Education will be the cornerstone for this RMP, not only for the disease, but an awareness of how to treat and how to diagnose some of the events that are seen with this. Obviously, the medication guide will be a key part to this, to be given every time a prescription is given to the patient.

The early access program will be the same as the one that is for the health care providers and, lastly, the patient/physician treatment plan will also be part of that.

[Slide.]

I will give you details on all of these in just a few moments.

[Slide.]

Let's start first, though, with what is the patient's access program? It will use -- what assessments rather will be used during this time? It will start with the patient access program. So, as soon as the product is launched, we will start this.

We will have enhanced pharmacovigilance program with detailed and very specific forms for 1A depression or a seizure is reported spontaneously through postmarketing surveillance, so that we can capture as much data as we can.

Being mindful that postmarketing is exactly what it says, it is voluntary. The physicians will be requested to fill out the form, but we cannot compel them to complete it

[Slide.]

Also, for those patients and physicians who are actively participating, we will do a survey of them to see how they are satisfied with the tools that we have.

Once we have a full commercial launch, we will have a prescription survey. Again, something that is currently being used in Europe, which we will fly here in the United States. I will show you some of the assessment tools that we have used so far with this.

We will also be looking from an epidemiology point of view, at both the health care

insurance claims data bases, both automatic and manual and, lastly, we have just reached an agreement with the American College of Cardiology, to institute a disease registry in collaboration with them.

Let me just show you a little bit about our experience in Europe to date. Specifically, with the UK prescription survey. As I told you before, rimonabant was approved in June of 06 in the European Union and launched in June of 06 in the UK.

Shortly after that, we did a prescription survey, one in which we consulted with physicians who are prescribing rimonabant, asked them to give us information on their last three patients to whom they prescribed rimonabant and provide us some specific details on that.

As we could see, in September of 06, approximately 1.4 percent of the patients who had been prescribed rimonabant had severe depression or a history of severe depression.

We reacted very swiftly to this,

reinformed our health care representatives or sales persons, as they are called, to reeducate the physicians that the inappropriate patient for the use of rimonabant is one with a history of severe depression.

The effectiveness of this was noted and the next time we did the evaluation, which is in November of 06, and you could see there was a reduction from 1.4 percent down to 0.4 percent of the patients having severe depression at baseline.

In the most recently completed analysis, this now has dropped to even less than 0.1 percent, demonstrating that we do have an effective way, through our risk management plan, to observe what the risks are and to try to minimize them through an educational process.

Clearly, what we see, though, is a risk minimization plan is not a static plan. It is one that is a dynamic plan needing and requiring constant revision. So, the implementation tools that we are putting together now are for the initial phase of the RMP.

We will use them. We will measure and assess their utility. We will review that information with our key stakeholders, which are physicians, patients, various societies, health care's authorities including the United States and others.

We will have a report which will be reviewed by those stakeholders, reviewed by the FDA, possible modifications, and re-implementation of those new tools, and then the process will start again.

[Slide.]

So, what are the key messages--and I said education was the key to what we were dealing with--what are the key messages that we want to get across?

First, we want to talk about the disease.

We want to talk as obesity is a chronic disease requiring long-term therapy, comprehensive treatment, always including diet and exercise, lifestyle changes, that the treatment of obesity itself is associated both with positive and

negative mood alterations; that obesity is associated with several comorbidities including not only hypertension, dyslipidemia and diabetes, but also the potential for depressive disorders and, lastly, depressive disorders should be recognized and their consequences readily diagnosed and treated appropriately.

[Slide.]

What are the key messages that we are going to provide on rimonabant? Again, at the time of the prescription, patients are to be screened for who is appropriate and who is not, and who is not are those patients with a past history of depressive disorders and/or suicidality, those patients who have a diagnosis of depressive disorders, whether treated or not, and those on current antidepressant or anti-epileptic therapy.

Obviously, other elements of the prescribing information, once agreed upon with the FDA, will be included as part of those tools. Clearly, one of the keys, as mentioned by Dr. Rosenzweig, is the disappointment of patients in

what they perceive to be the overall benefit, so prior to the initiation of therapy, there will be a treatment plan between the patient and the physician to set realistic expectations for what the weight loss could be.

We will be stressing the need to have a reassessment on an ongoing basis of those patients, at 1, 3, 6, 9, and 12 months following the first year of therapy. Obviously, as we are going on, these dates and times will be modified.

[Slide.]

As we said, depression was noted during the rimonabant treatment, so this is one of the things that we will clearly be identifying to the patient and their physicians, as well as the family members, to look for and any suspected treatment of depressive disorders should institute an appropriate therapeutic action, which would include the discontinuation of rimonabant.

[Slide.]

Now, what does this physician checklist look like? We have not yet fully agreed on what

this will look like. We will institute a dialogue with physicians and survey to gather the right information. But currently, conceptually, what we have is a form.

There is a two-sided form, and I will show you the other side in just a minute, where the physicians would be queried and making sure that they ask their patients the right question about the treatment for depression, previous history, and the treatment for the epilepsy.

Being mindful that many physicians often treat the patient, not only the primary health care provider. But it could also be the cardiologist. It could be a neurologist, et cetera. So all the information then would be gathered in one spot.

[Slide.]

What is it exactly that we are going to ask the physician to do? Again, on the back side, we are going to make it very simple, a very simplified form to be used, just to ask a very simple two-point question that has been validated, that during the past month, have you or have you

been bothered by feeling down, depressed or hopeless.

Obviously, this questionnaire has been validated and the reference is here. And have you been bothered a little, no interest or pleasure in doing things?

If either one of those are answered yes, then, further evaluation of the patient is recommended prior to the initiation of therapy with rimonabant.

As I said, there are two parts to this. One is the physician, the other is the patient. So, to that end, we are recommending a medication guide. In this medication guide, which will be prepared in accordance with the CFR, obviously agreed upon with the FDA, we will also be providing information to the patient and to their family, again stressing the need to be mindful of depression.

This wording will look very familiar to those of you who have participated in the previous evaluations of the antidepressants. It is

patterned very closely to that. So, we will use tools that are already in place to help us monitor for depression.

[Slide.]

Let's come back to the disease awareness program. Sanofi-Aventis is firmly committed that we will not institute any direct to consumer advertising for rimonabant for at least one year following the launch. We want to make sure that patients and physicians are well educated on the use of the product.

We will be providing, though, however, a web site which will educate patients about disease awareness--that is, the disease awareness of obesity--stressing again that diet and exercise and lifestyle changes are the most effective way for dealing with this condition.

[Slide.]

As I mentioned before, there is a unique opportunity here to involve both the patient and the physician in their treatment plan. It will consist of four elements. Obviously the physician,

health care professionals, patients and their families, and pharmacists. Material would be produced in a language that is appropriate for its intended audience, so the physician, the patient, whether it's in English or in Spanish, these will all be worked out.

There will be a suggested dialogue that the patient and the physician have at each one of their visits. The tools, which I will briefly identify now, are both the physician tool kit and a patient family tool kit, something tangible for them to have in their hands, as well as we will be looking at the feedback to monitor the effectiveness of this through monthly physician surveys and monthly patient surveys.

[Slide.]

So, what is this? What is this tool kit?

Well, the tool kit is a disease awareness, the U.S. package insert, the physician checklist, which I just tried to identify with you, an identification of what are those most frequently prescribed antidepressants and anti-epileptics, not

that physicians don't know what they are. But sometimes the list may be so long, we want to remind them of them.

We also wanted to give them and provide them tools for assessment of depression, as well as suicidality, and a reminder of what those other adverse events are, that are part of the approved package insert.

[Slide.]

It will be again for disease awareness and the medication guide, which is dispensed each time a prescription is given. They may or may not know all of the antidepressants or antiepileptics, so commonly used ones, including the generic, as well as the trade name will be provided.

There will be a self-assessment tool developed for the detection of depression and an agreement on the return visit schedule. And they will keep a treatment diary, something that they will have to monitor their progress as they go along.

[Slide.]

This is just a schematic diagram trying to indicate here, at the time prior to prescription were the two elements, and then at one month, 3, 6, and 9 and 12, the progress that the patients will make.

[Slide.]

Just as an example. What is a potential physician/patient dialog to look like? First, to talk about the benefit of rimonabant, have they had any benefit to measure the weight, to measure the height, weight, to adjust the diet and exercise program, prescription of any code therapies if necessary to treat other co-morbidities and, obviously, to be mindful of the adverse events especially those with depression.

On the other side, the dialogue should take place between the patient and again the caregiver or the family, looking again for the benefit, so charting their progress towards an agreed-upon goal realistically, as well as changes in their mood, dizziness, sleeping, feeling anxious, et cetera.

I talked about also a patient access program. What is that? This is a tool again to evaluate the appropriateness of the RMP. It will be a controlled launch; that is, we will introduce the product gradually into the marketplace.

Physicians again will be provided with educational material and the Lessons Learned from this will enable us to understand better, how to launch the product fully. What is it? This program will include 20,000 appropriately-trained and educated physicians. Each of these 20,000 physicians will enroll 10 appropriate patients to be treated with rimonabant, appropriate and not appropriate as we have identified.

[Slide.]

There is going to be an assessment based on monthly message recalls to make sure that the patient and the physician are using the product properly, the benefit-risk profile is being maintained and, again, just like we did in the UK, to have some follow-up, again tracking in the patient diary.

[Slide.]

As we did in the UK, we will also institute a series of prescription surveys. The one that I am going to display to you here now is one involving approximately 2,400 patients. It is a number that we have chosen based on the fact that we want to have 800 patients per sample. We want to take the three most recently prescribed patients from the physicians. And we want to collect this data in four month intervals, so that we have a good estimation of what is happening in these patients during the first year of launch.

Again, to make the modifications back to the RMP as we did for the UK.

[Slide.]

So, in summary, we have identified the three key elements of the RMP, those being the identified risks, those tools that we will use for the intervention, and an assessment.

Also, here should be included the re-evaluation of the RMP in a very iterative way, so that it will be a living document.

[Slide.]

Again, I come back to what I put on the very first introductory slides. Who is the appropriate patient to be treated with rimonabant?

Again, the emphasis is it is not everyone, so the physicians and the patients should take together the decision as to who is right for the treatment, not only in terms of the potential benefit, but also those in which we have identified some potential risks.

[Slide.]

Clearly, the sponsor is committed to working very closely with the FDA and other groups, both patients and physicians, to implement as quickly as possible following the approval of the product and RMP. That will address the growing and serious problem of obesity in the United States.

Thank you very much.

DR. GURAL: It would now be my pleasure to introduce Dr. Louis Aronne, who is Clinical Professor of Medicine at the Well Cornell Medical College and is Director of the Comprehensive Weight

Control Program at the New York Presbyterian Hospital.

Over the past 20 years, Dr. Aronne has been active in the research and treatment of obesity. Dr. Aronne was the editor of the NIH Practical Guide to the Treatment of Obesity, which we heard earlier this morning.

Dr. Aronne is also the past president of the American Obesity Society.

Dr. Aronne.

Benefit/Risk of Rimonabant

DR. ARONNE: Mr. Chairman and members of the Committee, I would like to conclude this morning's presentation with an evaluation of the benefit and risk of rimonabant. I would like to make four main points.

First, that obesity is a chronic disease which requires many different treatments, treatments we don't currently have. The pathophysiology of obesity involves overactivity of the endocannabinoid system. CB1 blockade thus addresses an underlying mechanism of weight gain

and fat accumulation, which translates into clinical benefits for the patient.

Second, that the patients I see, the high risk, obese patients with sleep apnea, diabetes, cardiovascular disease also seen by cardiologists, endocrinologists in clinical practice could benefit from rimonabant.

Third, that the risks associated with its use are manageable through health care provider and patient awareness of these adverse events, together with a clearly defined strategy to identify susceptible patients, and finally, an expeditious management plan for patients with adverse events.

Let me begin with the pressing medical need addressed by rimonabant.

[Slide.]

Obesity is the leading cause of both diabetes and heart disease. Current treatments for diabetes and heart disease don't address the underlying obesity and its many other complications.

Here we see the positive relationship

between weight and the risk of developing diabetes, hypertension, coronary heart disease and gallbladder disease.

Even within the normal range of weight, the relationship is positive. The relationship between obesity and diabetes is so steep it goes off this chart. See here, even within the normal range, it goes off this chart.

Accordingly, current guidelines for managing patients with diabetes and other obesity-related diseases specify that assessments of risk factors should include obesity and that risk factor reduction should include weight loss in obese or overweight patients.

[Slide.]

Here, we see the continuum of treatment options. First, we can do nothing to manage weight and, in my opinion, this is not an acceptable option. The real need is to treatment patients with multiple complications of obesity with a treatment for obesity rather than the 4 to 6 or more drugs often taken by patients with diabetes,

hypertension and hyperlipidemia. Several million Americans fit into this category.

When weight loss is achieved in this patient, the benefit is clear, because obesity treatment not only improves these diseases, but it also improves their joint problems, inflammatory markers, their sleep apnea and quality of life in a way that those other treatments just can't.

It can reduce the number of medications used and therefore, the side effects associated with the use of multiple drugs.

Now, in the non-pharmacologic domain, we have non-prescription herbal preparations and dietary supplements which make up the majority of the market. People use them because they have no options.

In this case, there is little evidence of benefit and safety. Diet, exercise and behavior is the treatment of choice, but it doesn't work as well as we would like.

Currently, two medications are available for use. They are underutilized, orlistat, because

of the possibility of gastrointestinal side effects, sibutramine, the possibility of increased blood pressure.

Compare that to the 11 classes plus combinations available for the treatment of hypertension.

At the extreme end of the spectrum, we have surgery. In evaluating the benefit and risk of rimonabant, one comparison could be with lap band surgery, which is now being evaluated as a treatment for those with a BMI as low as 30 with complications.

I think this comparison is an important one for it underscores how difficult it is to get our patients to lose and maintain weight loss. While lap band surgery produces about 17 percent weight loss in patients with a BMI less than 35, it is associated with a surgical risk of 8 percent and a mortality of 0.4 percent.

It is of interest that in the lap band registration trials, in which an operation is performed and a plastic device inserted, that must

be manipulated, only 77 percent of patients completed one year and 64 percent completed two years of the trial.

Twenty-three percent of patients required re-operation for complications including gastric dilation, band slippage, and erosion. At 36 months, 23 percent were lost to follow-up or had no information available, and 15 percent had the device explanted. Mortality was 0.5 percent.

The maximum weight loss was 18 percent over the trial. Based on the same type of analysis, weight loss with rimonabant would be 11 percent. I believe this comparison puts in perspective the weight loss, the possible complications associated with weight loss, and the difficulty we face in performing these types of trials.

[Slide.]

It is important to recognize that the weight regulating systems are redundant, biased towards weight gain and prevent weight loss. The endocannabinoid system is now known to be a

modulator of some of these pathways and it plays a role in the overall regulation of energy balance.

As you have heard, every animal model and several human studies have demonstrated an association between overactivation of the ECS and obesity. Given the relationship between stimulation of CB1 receptors and the pathophysiology of obesity, CB1 blockade is a logical and rational target for weight management.

Thus, in much the same way that an angiotensin receptor blocker reduces blood pressure, we can now block the receptor which plays a role in the pathophysiology of obesity. The result is an improvement in multiple comorbidities.

The use of CB1 blockers makes physiological sense.

[Slide.]

What are the actual benefits? In my opinion, the improvement in glucose, HbA1C, triglycerides, HDL cholesterol, blood pressure and inflammatory markers represents the best current estimate of efficacy, for we know that there are

surrogate markers of improvements in health outcomes, but there are other health benefits, as well.

So, while weight loss is indeed a critical outcome, the impact of the weight loss on comorbidities including an improvement in quality of life tells the real story of benefit, and they all go in the same direction towards improvement.

[Slide.]

Finally, and most importantly, is the issue of safety, a major concern of patients, clinicians and regulators. While we would like to have medications without side effects, that is just not possible.

The question then is how to minimize risk when you have a drug with the potential health benefits of rimonabant. The safety profiles of rimonabant has been characterized in clinical studies of over 7,000 patients and postmarketing data on more than 100,000 patients.

Treatment with rimonabant has been associated with a higher incidence of depression

and anxiety, especially in patients who have a past history of these disorders. Depression and anxiety are more common in the overweight and obese and these patients should be excluded from treatment with rimonabant.

I would liken this clinical decision to that of the decision to forego a bisphosphonate in an osteoporotic patient with an esophageal stricture, or a beta blocker in an asthmatic with coronary artery disease.

This is what we do in practice every single day. The health care provider makes a decision about treatment after reviewing the indications and contraindications of the treatments available, weighing the risks and benefits of the treatment.

[Slide.]

Here, you see a comparison of the same side effects compared within the class of obesity drugs. Nausea, depression and anxiety have been reported to some extent with other medications within the class and, indeed, medications in other

classes including those used to treat migraine headaches and skin disorders.

In my experience as an investigator, i have seen depression emerge in patients treated with drugs in this category. The onset of the depression was a few days to weeks after starting treatment. The patients we saw had a past psychiatric history. They felt fine within a few days of discontinuing the medication and, thus, in my experience, the adverse events have been manageable.

[Slide.]

In order to screen susceptible individuals and detect those who develop symptoms of depression and anxiety as soon as possible, a clearly defined strategy of education, screening and monitoring should be implemented.

Here, we see questions referred to earlier. We use questions like this, right now, as part of our initial evaluation because depression is a contraindication to treatment. So, this is an appropriate part of the initial evaluation of the

patient who is being treated for their obesity.

Appropriate labeling combined with a comprehensive educational and monitoring program where the patient and health care providers is an appropriate measure for minimizing risk.

[Slide.]

So, in conclusion, I see rimonabant as an addition to the very limited armamentarium of tools for managing overweight and obese patients with multiple risk factors.

It addresses the pathophysiology of obesity and its metabolic consequences. It addresses body weight and it improves multiple risk factors. It improves the quality of life. It may reduce the risk of developing type 2 diabetes. The safety profile has been defined, but we know that, as with any drug, the evaluation of safety is an ongoing process.

There is a plan for minimizing risk, which includes education of patients, health care providers, screening for depression and suicidality, strategies for monitoring and

management.

[Slide.]

Finally, let's apply insights gained from the Diabetes Prevention Program to the weight loss seen with rimonabant.

Based on data from the DPP, the weight loss achieved with one year of treatment with rimonabant, diet and exercise would reduce the risk of developing type 2 diabetes by 80 to 90 percent in those at risk.

Looking at this another way, it would more than double the number of people who did not develop diabetes compared to those on diet and exercise alone.

Rimonabant could thereby prevent or delay the associated microvascular and macrovascular complications we see with type 2 diabetes. Rimonabant has the positive attributes of a treatment option to address the medical needs of many of the patients that I see every day.

Given an effective method for screening out patients susceptible to side effects and a

clinically viable strategy for managing adverse events when they occur, I believe that rimonabant can offer a positive balance between the likely benefits and potential risks for a group of patients who need better options.

Thank you.

DR. GURAL: Mr. Chairman, that concludes our presentation.

DR. ROSEN: Thank you, Dr. Gural, and if you could stay up there, so that you or somebody of your sponsor will be able to address questions from the committee.

I would like to start with Dr. Gilman.

Clarifying Questions from the Committee

DR. GILMAN: I have two questions actually.

The first one relates to the slide showing quality of life in the RIO pooled ITT analysis. In our handout material, it is on page 42. It shows beneficial effects with respect to quality of life.

This is a pooled ITT, so they intend to treat the entire population. And yet that same set of

studies showed a 34 to 47 percent dropout rate plus a number of adverse events.

So, how do those two phenomenon jibe? These seem like very positive results and yet we have a huge dropout rate.

DR. GURAL: Dr. Rosenzweig, could you address that?

DR. ROSENZWEIG: So, your question is addressing the quality of life data and whether we take into account the dropout rates during this assessment? Is that the correct understanding?

DR. GILMAN: No, my question relates to the discrepancy that I see between a very positive set of data here in the bar graphs on my page 42, and yet there is a very high dropout rate and a very high prevalence in the study of people with untoward effects including depression, et cetera, et cetera. How do these two phenomena jibe?

DR. ROSENZWEIG: My understanding is that the patient expectations about their body weight loss is tremendously more than what can be delivered by a drug. They expect to lose a lot of

weight and then when they don't lose that body weight loss that they expect, they drop out from the trial.

So, we cannot capture that patient, and they drop out, and the one having an improvement. These data of the patients which are dropping out are still captured using the LOCF, so probably this is minimizing the effect, the beneficial effect of the quality of life.

DR. GILMAN: I don't think I made my question clear.

DR. ROSENZWEIG: Maybe I can ask Dr. Durrleman to come to the microphone and give his perspective on this.

DR. DURRLEMAN: Dr. Durrleman from Sanofi-Aventis.

The LOCF analysis that is being done to analyze the quality of life considers the last observation carried forward. Therefore, those few patients who discontinue for those adverse events are considered in this analysis with the last values they have under treatments. Obviously, what

happens to them following treatment discontinuation is not included in the quality of life assessment.

So, in a way, the data indicate that in the large majority of patients who do not experience psychiatric adverse events or other adverse events, possible negative quality of life in a few patients with adverse events.

So, here you have the full set of data.

DR. ROSEN: So, I guess the question is you don't track those patients after they fall out of a study to ask them their quality of life indices once they have dropped out of the study, correct:

DR. DURRLEMAN: This is correct, after the patients discontinue treatment, so the last observation is carried forward.

DR. GILMAN: Then, it is not true that this is the ITT data, this is incorrect, is that right?

DR. DURRLEMAN: What happens and it is a common problem in quality of life analysis is that when you have attrition, it is very hard to

indicate because the patients have discontinued.

DR. GILMAN: One minor question. What is it like to patients who are on drug and eat? Do they lose the appreciation for food? Do they just lose hunger? Can they enjoy their food? Can they taste their food?

DR. ROSENZWEIG: Yes, we have measured that during our clinical trial. The hunger is decreasing, but the enjoyment with food is maintained.

DR. GILMAN: Something I haven't really talked about is the dropout rate, and there is a 40 to 50 percent dropout rate in the four RIO trials.

Sort of a couple of related questions. Is the weight proportional to the original body weights, getting back to the expectations of people wanting to lose 150 pounds, if you started at 400 pounds, and you lose on the average of 5 kilos, that is not going to meet your expectations.

Number two, what is the pattern of the dropout rate, why did they drop out compared to the placebo and when? That hasn't been discussed at

all by you guys.

DR. GURAL: Some very interesting questions and comments. Dr. Rosenzweig, if you could address this and relative to our experience with reported literature for other products.

DR. ROSENZWEIG: So, your question is about dropout rates and when and why? Is weight proportional to the original weight loss:

Let me first cover the continuation and discontinuation rates at one year, if I can have the slide on. These are the completion rates across the four studies and, as you can see here, rimonabant 20 mg and placebo had about the same completion rate, in fact, a little bit more on rimonabant.

These were the dropout reasons for subject requests here. Adverse events, lack of efficacy for compliance and loss to follow-up.

When did the dropout rates occur was your question also. The dropout rates, and I don't have slides for this, but the dropout rates were more frequent during the initial part of the treatment.

During the first three months, the dropout rates was more permanent and especially due to subject request, both arms, yes.

Your third question is about the weight loss in terms of percent of body weight; is that correct? I think I have in the backup data, data about body weight loss in expressing percent from the initial body weight.

Would that answer your question?

DR. GILMAN: Yes.

DR. ROSENZWEIG: The body weight loss in terms of percent was about the same than the one expressed in kilogram, because the patients were, on average, 100 kg on average. So, a patient lost 4.7 percent of their initial body weight loss on rimonabant 20 mg as compared to placebo. The patients who were the heavier lost a little bit more than the patients of the lower BMI. There was 1 percent more body weight loss compared to the initial body weight in the patients with BMI over 40 as compared to the one with BMI less than 40. But the response in terms of body weight loss of 4

percent, you know--maybe I can go back also to the patients who met the criteria of 5 percent body weight loss, which is another way to look at this data, which I didn't present. It was in the briefing package.

Can I have the slide on, please.

These are the patients meeting the 5 percent decrease in their body weight loss as compared to the initial body weight that was in your point.

These are the figures of rimonabant 20 mg, 5 mg, and placebo in four RIO trials. As you can see here, on each of the trials, the proportion of patients matching this decreasing 5 percent of their initial body weight loss on rimonabant 20 mg was clearly very highly significantly different from placebo.

DR. ROSEN: Thank you.

Dr. Goodman, please.

DR. GOODMAN: I want to return for a moment to the quality of life measures, this time, though, the slide No. 82, which is on page 41, the

SF-36. I want to make sure I understand this figure correctly.

It appears that on the physical functioning there is an advantage in quality of life for rimonabant but, if you look at social functioning and role of emotional functioning, the role of emotional functioning and mental health functioning, you see actually deterioration in both groups but statistically greater in the study group.

Could you comment on that, if I interpreted that correctly, one, and, two, how do you explain that association, could patients at the same time, or would the same patients, be experiencing improvement in physical well being, but emotionally, they feel worse? Could you just clarify it, please.

DR. ROSENZWEIG: Your observation is correct. With this generic instrument of SF-36, there was a kind of changes in all directions, changes in physical function. There was also comparison to placebo, well, less of a decrease in

bodily pain as relative improvement.

There was also relative improvement with general health, deteriorating on placebo. But that is statistically significantly different on rimonabant. But you are right.

On the emotional role and the mental health, there was more decrease on the rimonabant 20 mg, and we looked at these data. And this is driven by the patients which experience the mood disorders described by my colleague, Dr. Paul Chew.

However, these differences that you ask, that are statistically significant, taking into account the number of patients that we have, the number of observations are at two points on this SF-36 scale and, really, when we looked at that patients with the mood disorders, you have a decrease of 20 in these patients, so the difference in these subsets of patients, they are really driving this difference that you see in the general population due to this difference, so whatever the mood disorders occurred on placebo or on rimonabant, there was a decrease of 20 in these

patients driving this difference.

Your second question was about how I reconcile these effects, is that correct?

DR. GOODMAN: Yes. I think you may have already partially answered that to say there was a contribution by the ones that mainly were experiencing depression.

DR. ROSEN: We have time for one ore question before the break. Dr. Proschan.

DR. PROSCHAN: I was wondering. You mentioned that people who go on antidepressants are discontinued. I wondered, is such a person counted? I assume they would be counted as having an AE by virtue of having to go on the antidepressant. But would that necessarily be a serious, you know, an SAE?

DR. GURAL: Dr. Chew. As Dr. Chew approaches the podium, clearly, according to the protocol of the completed Phase III protocols in the obesity, the RIO studies, any patient who experienced a depression and required antidepressant therapy was required by the protocol

to discontinue the study involvement.

DR. CHEW: Dr. Proschan, patients who develop depression regardless of whether they needed antidepressants was considered an adverse event, and the physicians were urged to do that.

The seriousness classification would be if it was medically important, required hospitalization, a prolonged hospitalization, was imminently life-threatening, so it would depend on the aspect of that.

Bud I did want to get back to one point, if I could, Mr. Chairman.

DR. ROSEN: We are running late, so I think we should wrap this up if you were satisfied with the response to that question.

DR. PROSCHAN: Yes. The only thing I just wanted to say is that you may be undercounting SAEs because that patient could have had an SAE later as a result of that depression, and you won't count that.

DR. CHEW: We did go back on all patients who had antidepressant therapy or neuropsychiatric

events, over 4,000 queries, 4,000 patients to specifically assess that point.

DR. ROSEN: Dr. Colman.

DR. COLMAN: Could the sponsor put up Slide 130.

I just wanted to clarify and put some of this into perspective. I don't know if this was mentioned, but this language from the sibutramine or Meridia label, it's another weight loss drug, this comes from the postmarketing report section of the labeling. If you read the first paragraph of that section, it says, "Voluntary reports of adverse events temporarily associated with the use of sibutramine was listed below. It is important to emphasize that although these events occurred during treatment with sibutramine, they may have no causal relationship with the drug."

In fact, we will be showing you some data later--it still is postmarketing data, but it is data from the same database, so that we can show you comparative data for orlistat, sibutramine and rimonabant, which I think is important.

I would also point out that in this same section of the sibutramine labeling, you will find event terms, such as heart arrest, increased salivation, hypothyroidism, hypoglycemia, nasal congestion and alopecia.

Another point I would like to make is sibutramine was originally developed as an antidepressant back in the early mid-to-late 1980s.

Apparently, it didn't pan out too well, but it is chemically, its mechanism of action is very similar to Effexor. It's a norepinephrine and serotonin reuptake inhibitor.

Now, during the original obesity trials for sibutramine, which involved about 3,000 patients up to a year, there were zero suicides, no complete suicides. Furthermore, the agency, as most people know, in the past year or two has been looking at antidepressants and suicidality in extensive detail and, as you know, the current labeling for antidepressants for adults for major depressive disorders, there is no warning about suicidality. It has been limited to pediatric

patients where they have seen perhaps a signal, and even that is debatable. But there is a labeling warning about suicidality in children taking antidepressants if they have major depressive disorder, and we did put some of that language in the Pediatric Section of the Meridia labeling.

So, I think those are important facts that were not brought out that need to be kept in mind.

DR. ROSEN: Thank you, Dr. Colman. We will reconvene at 20 minutes past the hour.

[Break.]

DR. ROSEN: We could reconvene if everybody would take their seats.

There has been a request to have the questioners from the committee identify themselves.

We have a remote viewing area for reporters and media, and they would like very much to have the committee members identify themselves prior to asking the question.

So, if all of us on the committee could remember to say who we are before we preface the question.

Let me just give you a brief update while people are getting to their seats about our schedule. What we are going to do now at 11:15 time, which is really 11:20, Dr. Karen Davis-Bruno is going to talk to you about the preclinical evaluation of rimonabant and then we will have time for questions, the lunch break will be at 12 o'clock, and at 1 o'clock we will hold the public hearing, the open public hearing at which three people will be testifying, followed by an FDA presentation by Dr. Egan.

I think without further ado, if everybody can take their seats, we will get started with the second part of the morning session, the preclinical evaluation by Dr. Karen Davis-Bruno from the FDA, Division of Metabolic and Endocrine Drug Products.

FDA Presentations

Preclinical Evaluation of Rimonabant

DR. DAVIS-BRUNO: Thank you. I have been asked to present today a nonclinical overview which will focus on the central nervous system toxicities associated with rimonabant.

[Slide.]

My presentation will include, first, a discussion of the role of the endogenous endocannabinoid system or ECS, followed by a brief discussion of rimonabant's pharmacology, focus on its mechanism of action, and then turn to an overview of the nonclinical toxicology studies focused on the central nervous system findings in various species, and then briefly conclude with a discussion of the clinical relevance of those central nervous system toxicities in the multiple species.

[Slide.]

The endocannabinoid system or ECS is a complex endogenous intercellular signaling system, which plays a modulatory role in a variety of functions in both the central and the peripheral nervous system.

The regulation of the endocannabinoid system in a variety of functions including energy balance, stress recovery, food intake and metabolic homeostasis are among the most extensively studied

functions of the endocannabinoid system. Indeed, you have heard a great deal about all of these earlier this morning as they function in the control of appetite and energy metabolism.

They have been implicated in the pharmacologic activity of rimonabant.

The endocannabinoid system is also involved in a number of other regulatory functions including cardiovascular effects and depressive effects, as well as modulation of the endocrine axis, the hypothalamic pituitary adrenal axis, and immune modulation.

I will focus my presentation on the neuroprotective effects of the endocannabinoid system, which are involved in the regulation of motor behavior, cognitive and memory functions.

[Slide.]

As you have heard earlier, the endocannabinoid system is comprised of a number of components including the endogenous ligands or the endocannabinoids. The structure of two of these endocannabinoids is indicated on this slide,

including anandamide and 2-arachidonoylglycerol.

Most of the endocannabinoids are lipophilic molecules and are derivatives of arachidonic acid, which is an important membrane constituent.

The endocannabinoids are synthesized on demand and they are not stored in vesicles like traditional neurotransmitters or traditional hormones. They act locally in an autocrine or paracrine fashion and are rapidly degraded following cellular reuptake in subsequent hydrolysis.

Endocannabinoids are versatile signaling mediators involved in a broad spectrum of physiological processes. The proteins involved in the synthesis, the membrane transport and the metabolism of endocannabinoids are also components of the endocannabinoid system but they are not listed in the slide.

The endocannabinoids bind to G-protein-coupled cannabinoid receptors indicated as CB1 and CB2. There are other non-CB1 and

non-CB2 cannabinoid receptors which have been recently identified but their roles are under current research investigation.

CB2 receptors are implicated in immune function and they have also been identified most recently in the central nervous system having originally been thought to be located only in the periphery.

The functions of CB2 receptors are less well understood than those of the CB1 receptors, which is our focus today. CB1 receptors are located in the central nervous system in the brain and in the spine, and also in the periphery in a variety of tissues including adipose tissues, skeletal muscle, liver and GI tract.

These peripheral receptors are also under active research investigation. CB1 receptors function in the regulation of food intake and energy metabolism, which is among the most extensively studied roles of the ECS, and you have heard a great deal about this.

Stimulation of CB1 receptors by cannabis

and its derivatives is associated with increased intake of palatable foods and has made the endocannabinoid system a therapeutic target for the treatment of obesity and for the generation of weight loss.

Rimonabant, which is our focus today, is the first in class, CB1 receptor antagonist in this system.

[Slide.]

This slide depicts the regional distribution of CB1 receptors in the central nervous system. There is a correlation between CB1 receptor presence in these important brain regions and the established regulatory roles of the endocannabinoid system which we have already discussed.

For example, basal ganglia and cerebellum are both involved in movement control and these regions have enriched concentrations of CB1 receptors.

[Slide.]

The hippocampus, involved in learning,

memory and stress, as well as the cerebral cortex involved in higher cognitive functions, are also enriched in CB1 receptors.

The hypothalamus and the medulla are both implicated in appetite control but, interestingly, the density of CB1 receptors in the hypothalamus is relatively low compared to the other brain regions.

This suggests that factors other than receptor density, such as receptor effector coupling efficiency, which we will discuss shortly, may be involved.

Lastly, the spine is involved in peripheral sensations including pain responses and also contains CB1 receptors. CB1 receptors are widely expressed in the brain and are present at different levels in different neuronal subpopulations and brain regions. There is apparently no strict correlation between the levels of receptor expression and function.

[Slide.]

We have discussed some of the modulatory roles of the endocannabinoid system and now we need

to understanding how it performs these roles. Briefly, depolarization of neurons leads to induction of endocannabinoid synthesis, which modulates the synaptic transmission via CB1 and other receptors.

The endocannabinoids act as retrograde signaling agents which selectively and restrictively decrease synaptic input onto a stimulated neuron and modulate the constitutive tone of the endocannabinoid system.

This retrograde neurotransmission is a process that challenges the traditional concept of one-way neural transmission.

On this slide you can see that CB1 receptors are present in both presynaptically and postsynaptically. They are also present on interneurons but this function is less well understood.

Essentially, postsynaptic depolarization opens voltage-gated calcium channels leading to an increase in intercellular calcium and this calcium then activates enzymes, which synthesize the

endocannabinoid.

Depicted in this slide is postsynaptic glutamate receptors which are linked to a specific endocannabinoid 2-arachidonoylglycerol, and this endocannabinoid then is released from the cell and binds to the presynaptic CB1 receptors.

CB1 receptors are generally considered inhibitory to neurotransmitter release. The inhibition of neurotransmitter release is mediated through a complex interaction with G-proteins, which modulate inhibition of the presynaptic cells' calcium channel, thus, decreasing the probability of neurotransmitter release.

This retrograde neurotransmission can occur at both excitatory synapses, such as glutamatergic synapses, as well as inhibitory synapses, such as GABAergic.

Endocannabinoids can serve as inter- and intra-cellular signaling molecules. The literature supports endocannabinoids as versatile signaling mediators that act in a paracrine/autocrine manner independent of synaptic transmission in various

cells including adipocytes, hepatocytes and in glial cells.

[Slide.]

The pharmacology of the endocannabinoid system is very complex and it can produce effects on several levels including those at the tissue level, at the cellular level, and at the molecular level. We have already discussed those functions at the tissue level including the effects on motor behavior, cognition, memory and sensory effects.

At the cellular level, endocannabinoids can affect neurotransmission specifically through this somewhat unique mechanism of retrograde neurotransmission. This can lead to modulation of neurotransmitter activity of various neurotransmitters including GABA, dopamine, serotonin, glutamate, effects on the vanilloid receptor, the NMDA receptor, the acetylcholine, norepinephrine, anorexin 1. These are all based on literature.

Moreover, you have seen in the previous slide that endocannabinoids can affect ion channel

function. There are a variety of calcium channels that are affected, as well as potassium channels, and the literature indicates that even sodium channels may be affected through this system.

What I haven't discussed is the complex interactions of CB1 receptors with other central nervous system receptors, such as specifically forming multimeric interactions of CB1 receptors with other CNA receptors either with other CB receptors forming homomeric complexes or forming hetromeric complexes with dopamine receptors, opioid receptors and adenosine receptors.

This can significantly increase the complexity and the pleiotropic effects that can be generated by the endocannabinoid system. On the molecular level, pleiotropic effects can occur as far as signal transduction effects go in that endogenous endocannabinoids inhibit the activity of adenylate cyclase and the phosphorylation pathway of protein kinase A, as well as cause stimulation of a variety of map kinases. These two functions together lead to effects on gene expression.

Moreover, there are multiple G-proteins that are coupled to CB1 receptors, and this effect really depends upon the ligand that you look at, the tissue that is involved, as well as the dose used as many of the endogenous endocannabinoids, especially anandamide and THC are reported to have U-shaped dose response curves.

The multiple G-proteins link to particular CB receptors and those G-proteins can have multiple effects in among themselves.

[Slide.]

Our understanding of the endocannabinoid system, or ECS, has been limited by the lack of selective pharmacologic tools until the advent of rimonabant as a selective CB1 antagonist.

Rimonabant has been described in the literature as having partial agonist and inverse agonist activities. Its role as an inverse agonist as you have heard earlier refers to its ability to module the constitutive ECS tonicity.

It is thought to shift the CB1 receptor from a more active to an inactive state, resulting

in an overall decrease in ECS tonicity. This slide graphically depicts a typical dose-response curve demonstrating what a full agonist and antagonist and an inverse agonist would do.

Rimonabant binds at the agonist receptor binding site and it thought to result in opposite effects, that is, to generate negative intrinsic effects as you heard in Dr. Mackie's presentation.

Generally, inverse agonists are effective in receptors that have an intrinsic activity, such as the cannabinoid receptors. It is has also been originally described for GABA, benzodiazepine receptors. Again, the effect that you see depends upon the ligand you look at, the tissue you look at, and the dose.

Rimonabant can also elicit effects that are independent of the CB1 receptor, for example, rimonabant can displace ketamine at the PCP binding site of the NMDA receptor with similar micromolar affinities.

[Slide.]

So, there are three mechanisms that have

been proposed to explain rimonabant activities. The first mechanism is that rimonabant can compete with the endogenous endocannabinoids for CB1 receptor binding.

The second mechanism involves inverse agonism resulting from the negative modulation, the CB1 receptor constitutive activity, and this is thought to occur predominantly through allosteric effects, moving the receptor from a more active or on state to a more inactive or off state.

The third mechanism that has been proposed is that CB1 receptor independent mechanisms, as you have heard earlier, the antagonism of endogenous adenosine at A1 receptors can also occur.

It is important to keep in mind that based on Dr. Mackie's comment this morning, that the animal studies have shown that there is clearly distribution of rimonabant into the central nervous system of particularly rodents, and that the concentration based upon radioligand studies have shown there is approximately a 2-fold accumulation in rat brain tissue relative to plasma.

So, if you look at the IC50s for these particular receptors, it is potentially possible that you could achieve concentrations of rimonabant that are near the IC50s for these other non-CB receptors.

[Slide.]

There is sufficient evidence to demonstrate a complex pharmacologic profile of rimonabant and its interactions with the endocannabinoid system. Blockade of the ECS orexigenic stimulus either in the central nervous system or in the periphery may be desirable with obesity, but pleiotropic central nervous system functions under ECS regulation would also be antagonized by rimonabant, resulting in dysregulation of important nervous system functions.

This is consistent with the central nervous system toxicities that are seen in animals at clinically relevant exposures following rimonabant treatment. Rimonabant, acting as an antagonist at the CB1 receptor interacts with the

ECS modulatory functions, leading to a number of effects that are both desirable and undesirable.

The adverse effects that are seen in animals include seizures, tremors, impaired movement, sleep disturbances, hyperesthesia, which is increased sensitivity to touch, anxiety and hyperexcitability.

They occur at the same exposures that cause the desired effect, which is to decrease appetite, to decrease food intake and to result in a decrease in body weight.

The clinical presentation that you will hear this afternoon will focus on the findings of depression and suicide, which can occur through the endocannabinoid system dysfunction, but are not readily assessed in standard animal models.

The endocannabinoid system is a complex modulatory system. It is under active investigation and we don't understand all the functions that it participates in.

The role of CB1 receptors in peripheral regulation of energy intake in adipose tissue,

skeletal muscle, and delivery in the GI tract, are indicated as tentative in the bottom part of this slide, and this is because the decrease in body weight effect can lead to these other beneficial effects in and of itself.

It may be through CB receptor interactions of rimonabant in the periphery, but it could be a direct effects of the decrease in body weight in and of itself, and the tentative nature reflects the fact that the peripheral function of CB1 receptors is under active regulation.

[Slide.]

This slide summarizes the effects of the endogenous endocannabinoids on motor effects, sensory effects and behavioral effects. This column shows the constitutive effect or the effect of endocannabinoids or endogenous endocannabinoids agonists.

This column shows you the effect in the presence of rimonabant, so if you look at regulation, modulation of motor effects, the constitutive effect of the endocannabinoid system.

It's a decreased activity and result in an anti-convulsant effect.

In the presence of rimonabant we see the incidences of seizures, tremors, and both impaired and decreased movement. If you look at sensory modulation, the ECS system is generally thought to decrease pain. In the presence of rimonabant, we see hyperesthesia, decreased body temperature, hyperexcitability and an increase in startle response.

If you look at behavior, the constitutive effect of the ECS system is an anti-anxiety effect, also associated with somnolence and an orexigenic stimulus.

With rimonabant we see signs of anxiety, sleep disturbances and an anti-orexigenic response.

[Slide.]

CB1 receptors are conserved across animal species from rodents to primates including, for that matter, reptiles and birds. This conservation is evident by a similarity in central nervous system regional distribution and a similarity of

receptor homology, and in regard to ligand binding affinity.

Thus, the conclusions of this are that the animal models have clinical relevance, and, in fact, you heard a great deal this morning about the mechanism of action of rimonabant and its ability to decrease weight, and those effects were worked out in animal models.

Thus, if animal models are sufficient for demonstration of efficacy and the mechanism of action of the beneficial pharmacologic effect, they are also relevant, I would argue, to identify the toxicities.

[Slide.]

So, if I could summarize. The key points in CB1 rimonabant receptor pharmacology, it is that the endocannabinoid system has pleiotropic neuromodulatory functions.

The endocannabinoid system is involved in the regulation of central nervous system activity through CB1 receptors.

Both the CB1 receptor sequence and

distribution are highly conserved across species.

Rimonabant is a CB1 receptor antagonist with a complex pharmacology and similar affinity across species.

[Slide.]

This slide summarizes the nonclinical toxicology studies involves in support of rimonabant's clinical development program.

Generally a standard package of nonclinical studies was presented by the sponsor including pharmacology studies, general toxicology studies in a variety of species including mice, rats, dogs and monkeys.

Chronic toxicology studies were done in the rat and in the monkey with durations of six months in the rat and up to one year in the monkey.

Two-year rat and mouse carcinogenicity studies were performed with lifetime daily exposures of rimonabant, followed by a standard battery of genotoxicity studies, as well as the standard battery of reproductive toxicology studies in both rats and rabbits.

The results of these studies suggested that the central nervous system was a major target organ of concern. Although the nonclinical data showed signals of central nervous system toxicity, significant clinical experience existed for another more serious indication when the application was submitted and, thus, it was the more advanced clinical data which supported further clinical development for this proposed indication.

[Slide.]

This slide shows a summary of the lowest observed adverse effect level for various CNS toxicities shown across various species.

If you look at the lowest exposure resulting, for example, in mortality, you can see that rodents and rabbits, this occurs at or very close to the human therapeutic exposure following a 20 mg clinical dose. In monkeys and dogs, a slightly higher exposure would be needed to demonstrate mortality.

Likewise, convulsions occurred in mouse, rat and monkey but generally at exposures that were

less than 3 times the human clinical exposure.

The convulsions weren't observed in the dog, but tremors were. The tremors could be partial seizures that were observed at 4 times the human therapeutic exposure. If you look at the rat, and you look at the spectrum of CNS toxicities that are seen, you can see it at all the central nervous system toxicities that are observed including mortality, convulsion, tremors, motor effects and aggressiveness all occur at the human therapeutic exposure.

It is important to note that all the animal models that were used in these toxicology studies were healthy normal animals and that the central nervous system toxicities were observed as part of the twice daily clinical observations performed during the design of those toxicity studies.

If you look at motor effects or rather motor dysfunction, it occurs across species at less than or equal to 5 times the human therapeutic exposure and, although less frequently observed in

the toxicity studies, aggressiveness and anxiety were also observed at low exposure multiple relative to the human therapeutic dose or human therapeutic exposure rather.

[Slide.]

Because of time constraints I will focus the remainder of my presentation on the seizure data although clearly, this is not the only central nervous system toxicity that was observed in animals.

CB1 receptors have been shown to mediate many of the anticonvulsive effects of endocannabinoids and to play an important role in regulating synaptic transmission. The toxicology data suggests that rimonabant antagonizes these effects by disrupting the endocannabinoid system's constitutive anticonvulsant tone and subsequent regulation of neuronal excitability possibly through competition with endocannabinoids for receptor occupancy.

[Slide.]

This slide shows that there isn't an

adequate safety margin for convulsions or tremors in animals, and it occurs in various species.

This is based upon the No Observed Adverse Effect Level expressed as a dose in mg/kg in the various animal species relative to the human therapeutic exposure based on either total exposure or area under the curve, or compared to a Cmax, the highest plasma level based on a 20 mg/day clinical dose.

In animals, convulsions and tremors were seen at exposures at or below the therapeutic exposure in humans. The safety margin, as noted below, refers to the animal divided by the human exposure at which there is an absence of convulsions and tremors in the animals, so it is another way of looking at the previous table.

[Slide.]

This slide shows the progressive nature of the seizure incidence at lower doses with longer durations of treatment in the mouse, the rat and the monkey.

If you take the mouse, in the acute

studies, 2,000 mg/kg were needed to demonstrate convulsions. If you look at the subacute toxicity studies, those are studies that are less than 6 months duration. The dose, to cause a convulsion, decreases to 120 mg/kg/day.

Similarly, if you go to the chronic studies, which are lifetime exposures, convulsions are seen at 16 mg/kg/day.

Similar effects are seen in the rat if you go from the subacute studies, 16 mg/kg with demonstrated convulsions. Chronic studies, this dose gets reduced down to 6. The monkey, the effect is less dramatic but, nonetheless, it's reduced with chronic duration of dosing.

[Slide.]

This slide shows the dose dependent incidence of seizures in both male and female rats following lifetime exposure to rimonabant.

Clearly, you can see low dose, mid-dose, high dose.

There is an increase in the numbers of animals experiencing convulsions.

The low dose, it is important to note, is

1 to 2 times the human clinical exposure.

[Slide.]

Studies were performed that directly examine the effect of rimonabant on seizure induction. This slide from the sponsor summarizes the results of such a study.

Here, rimonabant at various doses, 10 mg/kg, 30, and 100 mg/kg potentiates the tonic convulsions and mortality in a mouse seizure model.

There is not much of an effect on clonic convulsions compared to control. But if you look at the tonic convulsions, there appears to be a trend toward potentiation. It is not statistically significant and it is clearly not just related, but it's there.

Similarly, if you look at mortality and you look at potentiation, there is also a trend towards potentiation at the higher doses. This seizure model, the seizures are induced with PTZ, which is pentylenetetrazol. It's a GABA agonist. It's a standard model.

The doses tested of rimonabant, shown in

this slide, are below the human therapeutic exposure at 20 mg/day based on the clinical dose.

[Slide.]

This slide summarizes some key points in the observed seizure findings in multiple species at or below the human therapeutic exposure following rimonabant treatment in animals.

Rimonabant blockage of CB1 receptors appears to influence the anti-convulsant tone of the endocannabinoid system. Rimonabant induced dose-dependent seizures in association with CB1 receptor antagonism in multiple species. Seizures were dependent on the dose and the duration of rimonabant treatment and, moreover, the seizures occurred at animal exposures that were equivalent to the systemic exposure in humans at the proposed clinical dose of 20 mg/day.

[Slide.]

We have experience with other CB1 receptor antagonists that are currently under development. Central nervous system toxicity is observed in some of these other applications, but it is observed

generally at a greater than 10 times therapeutic exposure.

CNS toxicities that are observed include convulsions, tremor and motor dysfunction. This suggests that rimonabant differs from the others in the class by its narrow therapeutic index. Specifically, the exposure that causes the desired pharmacologic effect, that is, weight loss, is very close, if not the same, as the exposure that causes the central nervous system toxicities.

Because of this narrow therapeutic index, the central nervous system toxicities that are seen in multiple animal species would be anticipated occur at clinical exposures in people. You will hear more about that this afternoon.

[Slide.]

This slide summarizes the clinical relevance of the central nervous system toxicities seen in the nonclinical development plan. Generally, what you see is the exposures causing weight loss in the mouse, rat, monkey, dog and rabbit. All are at or below the human therapeutic

exposure. Relative to the observed central nervous system toxicities of mortality, convulsions, tremor, motor effects and anxiety.

Again, the data is expressed as the animal exposure at the NOAEL relative to the clinical exposure at 20 mg/day. The decreased body weight and the central nervous system toxicities occur in multiple species at similar drug exposures.

[Slide.]

So, if I could summarize.

Central nervous system toxicity occurs in multiple species at therapeutic exposure levels based on a 20 mg proposed clinical dose.

Dose-dependent central nervous system toxicities occur as a result of antagonism of the CB1 receptor and disturbance of the endocannabinoid system homeostatic regulation.

The plausible mechanism of action associated with weight loss appears associated with central nervous system toxicity.

Other drugs in the class show similar toxicities but occur at much higher animal

exposures.

There are limited, if any, differences between exposures generating the desired pharmacologic effect and those associated with significant animal toxicity, that is, seizures and mortality, motor dysfunction, anxiety, aggressiveness, supporting the clinical relevance of the central nervous system toxicity.

[Slide.]

In conclusion, rimonabant is a first in class, CB1 receptor antagonist for the management of obesity.

Sufficient information exists to demonstrate a complex pharmacologic profile.

Blockade of the endocannabinoid system-mediated orexigenic stimulus may be desirable for obesity, but a similar blockade of other CNS functions under regulation by the endocannabinoid system would not be desirable.

Studies in relevant animal species show CNS toxicities at clinically relevant therapeutic exposures.

We are not alone in our conclusions and that the European Regulators in 2006 noted, and I quote, "Nonclinical studies could provide no reassurance regarding margins to the clinical exposure. Consequently, the safe use of rimonabant has to rely more on the clinical safety data and post-approval pharmacovigilance programme."

The central nervous system adverse effects are consistent with the mechanism of action and are reported in the clinic and in postmarketing reports.

Thank you.

DR. ROSEN: Thank you, Karen.

Clarifying Questions from the Committee

DR. ROSEN: The Committee now is open for questions. I will start.

It appears that the rodents are more sensitive than the larger animals; is that correct?

DR. DAVIS-BRUNO: That is an accurate assessment.

DR. ROSEN: In the seizure models with the

PTZ induction, have you tested to see if other inbred strains of mice are more sensitive or less sensitive? There are some inbred strains that are more prone to seizures where you don't have to induce them with a drug.

DR. DAVIS-BRUNO: I don't know. I am not aware of specific strains, specific studies, that have been done with rimonabant. But perhaps Sanofi wants to comment on that.

DR. ROSEN: Yes. Dr. Hirsch.

DR. HIRSCH: Two brief questions. One is the mortality that you have listed. Is that due to the things that --

DR. DAVIS-BRUNO: I think that could be implicated, sure. They seize.

DR. HIRSCH: Were there any other causes of mortality?

DR. DAVIS-BRUNO: There are no lesions, there are no histopathological lesions observed in the toxicology.

DR. HIRSCH: Question 2. Long-term studies on animals, for example, brain,

neuropathology at 1 year, 2 years.

DR. DAVIS-BRUNO: There are no observable dose-related histopathological lesions that could explain what we see.

DR. HIRSCH: So, there are no relevant long-term animal studies to indicate what might happen, the ones on rimonabant for 5 years.

DR. DAVIS-BRUNO: Let me be clear. In general, chronic studies are usually 6 months to a year duration daily dosing in rodents and in non-rodents, that is part of the toxicology package.

There were also carcinogenicity studies which were lifetime exposure, lifetime daily exposures, which were performed by the sponsor. Basically, you wouldn't expect to see histopathological lesions if the cause of death, for example, is seizure, and you don't see it.

DR. ROSEN: Other questions from the Committee?

DR. CARPENTER: Tom Carpenter, Yale.

I wondered if specific attention to

plaque-like lesions or multiple sclerosis-like findings were employed in these post-death analyses?

DR. DAVIS-BRUNO: Generally, toxicology studies do a couple of sections through brain, spinal cord, et cetera, et cetera, and there were not any lesions that were found. That is not to say that if you designed a study to specifically look at that, you might see something. But they weren't observed.

DR. ROSEN: Dr. Kreisberg.

DR. KREISBERG: Bob Kreisberg. I know you didn't touch on this, but you did allude to it. Do you have any information about the long-term cardiovascular effects?

DR. DAVIS-BRUNO: There were effects that were noted in some of the original safety pharmacology studies, in Herb[?] channels and affecting in vitro type preparations.

They also I believe did a telemeter--it was either a dog or a monkey study--and that did not show effects, so we weren't concerned about a

cardiovascular signal in the nonclinical data. It was addressed.

DR. CIRAULO: Dom Ciraulo. Again, you didn't touch on this, but while we are discussing animal models, could you talk about any animal models of depression, has that been screened?

DR. DAVIS-BRUNO: I am not aware of the sponsor performing any specific depressive animal models although they are available.

DR. ROSEN: Dr. Goodman.

DR. GOODMAN: Are you accepting questions to the sponsor or just the FDA at this point?

DR. ROSEN: I think it is to the FDA at this stage, yes.

Other comments for the FDA?

Karen, I wanted to ask you to clarify that--because I think there is a bit of confusion about the physiology of the CB1 and CB2--so it appears that both the CB1 and CB2 are found in the periphery, and CB1 is found centrally.

Do you have any sense of which--what is activated predominantly or it is a mix of CB1's

centrally and peripherally that are having the major effects?

DR. DAVIS-BRUNO: That is really hard to address, because rimonabant is distributed centrally and peripherally, so we don't have a specific antagonist that isn't excluded from the blood-brain barrier, so that we could look at some of these peripheral effects. But that is under active research investigation.

DR. WOOLF: Paul Woolf.

Is rimonabant concentration in the brain enhanced or is it simply reflective of peripheral levels? Is there active transport into the brain?

DR. DAVIS-BRUNO: Rimonabant?

DR. WOOLF: Yes.

DR. DAVIS-BRUNO: Yes, it is transported into the brain. In fact, the rat brain tissue was reported with radiolabeled rimonabant to accumulate 2-fold relative to the rat plasma, so it is clearly distributed.

DR. ROSEN: Other questions or comments from the Committee?

Karen, anything else from your end?

DR. DAVIS-BRUNO: Not from me.

DR. ROSEN: Dr. Colman?

Okay. This adjourns the morning session.

We will reconvene at 1:00 p.m. for the Open Public Hearing.

[Whereupon, at 11:55 a.m., the proceedings were recessed, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. ROSEN: The first order of business this afternoon will be the public testimony. We have three individuals that I will introduce. Then we will go to a talk on the clinical efficacy and safety by Amy Egan from the FDA.

Right before that, we will have just a point of clarification from Karen's presentation from this morning looking at the relative toxicities of human versus the other animal models.

We have had some questions about that from the committee. So Karen is going to graciously come back up and show one or two slides.

Open Public Hearing

DR. ROSEN: I just have to read this.
"Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing Session of the Advisory Committee meeting, FDA believes it is important to understand the context of an individual's presentation.

"For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors.

"For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking."

So we have three people who have asked to talk. The first one is Dr. Sidney M. Wolfe. He will give the first presentation. Sid, could you just reintroduce yourself for the people who are in the remote room.

Sidney Wolfe, M.D.

DR. WOLFE: I am Sidney Wolfe, Health Research Group of the Public Citizen. The presentation was done collaboratively with Dr. Elizabeth Barbehenn, who used to be in the Metabolic/Endocrine Division of FDA at one time, and Ben Wolpaw who is a summer researcher with us.

I do not have any financial conflicts of interest.

The elusive idea of a magic-bullet drug that has a benefit mediated through its action on one receptor site, yet is devoid of risks at a myriad of other sites in the body, is, once again, evident with the discussion you have heard on rimonabant.

We have had recent examples including Vioxx, Rezulin and Redux where they were approved for a benefit on one site and then, in the case of Vioxx and Redux, they caused cardiovascular damage, in the case of Rezulin, liver toxicity.

But where else in the brain or other parts of the body are these CB1 cannabinoid receptors which rimonabant inhibits located?

You have heard, and I will just briefly go over, just within the brain, olfactory and cortical regions, neocortex, pyriform cortex, hippocampus, amygdala, basal ganglia, thalamic and hypothalamic nuclei, cerebellar cortex and so forth in the periphery of the autonomic nervous system, liver, muscle, GI tract, adipose tissue, pituitary gland, reproductive tissues and a lot of interesting work is going on now in terms of the effects on the cardiovascular system.

A recent review on the pharmacology of this system said, "CB system involved diverse physiologic functions that include roles in stress recovery and the maintenance of homeostatic balance. Such roles include, for example, neuroprotection." There is an interesting study just published in the last week or so in the animal model showing that you impair the neuroprotective properties of the cannabinoid system by using a blocker of it as in rimonabant.

"Modulation of nociception, regulation of motor activity, control of certain phases of

memory--"there was certainly some clinical evidence on that you have heard this morning--"modulation of immune and inflammatory responses, influence on cardiovascular and respiratory system and antiproliferation of the tumor cells."

Given the multiple sites in the brain with CB1 receptors, the extraordinarily broad kinds of psychiatric dysfunction caused by the drug, and we use this phrase "caused" carefully because these are randomized controlled trials where there is no other explanation, the myriad of psychiatric dysfunction caused by the drug in addition to which you have heard the statistically significant increased suicidality and other depressive systems are not surprising.

As seen in the table on Page 2, significant increases in anxiety, insomnia, panic attacks and almost significant increases in aggression, also seen in animal studies, and agitation in patients given 20 mg of rimonabant versus patients given a placebo.

In addition, significantly more patients

getting rimonabant required a sedative or tranquillizer or an antidepressant for adverse effects caused by the drug. This is during the course of the trial. Some of these increases are in a range, in terms of both the increase and the absolute values, they are much in excess of even the suicidality data.

For example, anxiety went up from 2.5 percent in the placebo group to 6.02 percent in the rimonabant group with the p less than 0.001. Insomnia went up also quite significantly, up 1.8-fold. Twice as many people required sedatives or tranquilizers. And the six-fold increase in aggression, not quite statistically significant but, again, concordant with the animal findings.

The evidence for increased suicidality and depression is a particular concern for a drug targeted towards the obese population that has been shown to have a significantly higher incidence of depression and eating disorders compared with non-obese individuals.

The question has been raised as to whether

or not the patients studied accurately reflected the psychiatric makeup of the obese population that we would be expected to see rimonabant treatment. The four studies, again in this table here, give information on the Hospital Anxiety and Depression Scale, HAD, data showing mean pre-treatment depression scores of approximately 3. This is in the patient population studied. The depression portion of the scale is out of an average score of a possible 21 points where a probable disorder is indicated by a score of above 8 to 11.

The average score of 3 is well below the mean value for the general population of 3.68. Given that the obese population has been found to have a 20 percent higher incidence of depression compared with the non-obese population, this number seems artificially low. Part of it may be due to the exclusion of certain groups of depressed patients. Whatever it is, it may diminish the information that we get from the study. The increases in depression and other things might be even greater if we had a more typical population

even though you have heard they are going to exclude these kinds of groups. This is easier said than done.

A related concern of significant importance is the exclusion in all RIO studies of patients on anti-depression medication. Between 2004 and 2006, 30 percent of all patients receiving phentermine, orlistat, sibutramine or diethylpropion had a concurrent prescription for an anti-depressant medicine. These are drugs used for treating obesity. This strongly suggests that patients would, if this would be approved, end up taking anti-depressants and rimonabant in tandem with unknown consequences.

Another problem with the clinical studies is the fact that there was a huge dropout rate. This was not presented by the company, but the range of dropouts in the four RIO studies was between 32 and 45 percent. This limits the significance of their findings in the debate over the safety and efficacy of the drug.

The high discontinuation rate obviously

could work both on the side of safety and efficacy.

You might get a better picture because of the dropouts of its effectiveness and a more benign picture of the safety profile.

Combined with other questions that have arisen during the methodologic quality of the four studies with regard to method of randomization, allocation, concealment and blinding, high attrition rates serve to throw conclusions on safety and efficacy into doubt, as I just said.

Reproductive and other preclinical animal effects. In its posted briefing document that went up on the Internet two days ago, Sanofi describes preclinical animal studies as follows: "In a comprehensive program of nonclinical studies, rimonabant was shown to have very limited potential to induce toxicity. No specific target organ pathology was identified in the completed animal studies."

This statement is, at best, misleading and more likely it is just dishonest. I will now read from a document that is up on the website of the

EMA, the European equivalent of the FDA.

"Amongst other things, in the area of reproduction, decrease in corpora lutea and implantations, decrease in viable fetuses,"--these were at doses very close to the human dose-- "increased pup mortality, decreased litter size in rabbits, and increased birth defects."

In addition to that, and these things are actually in the label on the drug in Europe--in addition there were a number of other problems including liver toxicity, genotoxicity, chromosome aberrations in lymphoma cells, mouse lymphoma cells, carcinogenicity in female rats, and hyperexcitability or aggressiveness, as I mentioned before.

The case of cannabinoid regulation of implantation and fetal development should also be taken as an example of how limited an understanding scientists have of the role of this widely dispersed neurotransmitter system. Rimonabant is the first drug in its class to be used in humans and there are many important questions that remain

unanswered.

It is interesting; the company recommended, and I have no doubt that that is what they would like to have happen, that long-term administration is required. This raises a whole issue about long-term effects both in terms of efficacy and safety. Of the studies performed to date, two had a duration of 2 years. Others were 1 year. Because rimonabant is the first drug in its class, no data evaluating the long-term effect in antagonizing this widespread cannabinoid system.

Weight loss while on rimonabant is regained after discontinuation of use which means that, if the drug is to be effective at all, it will have to be prescribed on a long-term basis as the company said this morning.

Given this fact, a complete lack of data on rimonabant use in humans over an extended period of time is cause for significant concern.

I don't have time to--how much time do I have left here? Two minutes? So I do have time. The literature on animal studies done with

rimonabant contains ominous indications of issues that might arise as people continue using the drug for longer periods of time. Zimmer, who was a fellow at the NIH for a while and is back in, I believe, Austria, now, has reported that CB1 knockout mice--these are mice that are missing this receptor which, in some ways, may be the same as knocking out the receptor with rimonabant--have significantly increased mortality due to "spontaneous deaths of unknown causes."

Zimmer, an expert in cannabinoid-system research, has also noted that the same strand of CB1-deficient mice exhibited increased loss of neurons with aging. Although this does not generalize directly to rimonabant use in humans, there is still cause for concern in the absence of studies evaluating the effects of long-term CB1 antagonism.

Other studies have shown clear effects of the CB1 receptor on the cardiovascular system in producing hypotension and bradycardia which, one would imagine, might be the reverse. It is

interesting, this morning, and other times, looking at some of these data, the expected reduction in blood pressure that you would expect in obese people when they lose weight was not found as significantly and this could conceivably be related to the fact that you are having some hypertensive effect of the drug.

A recent, very thorough, review of rimonabant published last year by the Cochrane Collaboration, which started out in Oxford but which now has branches in the United States, concluded that, one, the average weight loss is "modest" and, two, more rigorous studies about efficacy and safety are required to "fully evaluate the benefit/risk ratio of this new drug."

We strongly agree with this statement and it is a statement that clearly requires the rejection of the approval of this drug because of a lack of ability to fully evaluate the benefit/risk ratio of the drug.

I would just like to comment on what you heard from Dr. Davis-Bruno this morning, animal

models have clinical relevance, and you have seen, in a number of areas, where they do and I suspect that we would, unfortunately, see more if they had looked more carefully. Hopefully, we will not see it when the drug is not approved.

Thank you.

DR. ROSEN: Thank you, Dr. Wolfe.

The next speaker, it is my pleasure to introduce Lynn McAfee from the Medical Efficacy Council on Size and Weight Discrimination. Lynn?

Lynn McAFFEE

MS. McAFFEE: The Council does not take any funding from the diet industry, anything in the diet industry.

I wanted to just make some informal remarks to you today partly on social issues and to comment on some of the things I have heard, some of which are reassuring and some of which are just really scary.

First, I want to talk about the environment in which consumers will be making decisions to take this pill. Just in this room,

also, there is an enormous amount of weight prejudice in this room. I think we all know that.

We have tremendous job discrimination pressures which are, I believe, getting worse based on the claims that we have been getting in our office.

Social discrimination, just in terms of we marry less. Educational discrimination. You can go on and on. Even rental discrimination has been found. And nothing is really being done about it.

We are finding that, when we are saying, "Oh, that is not a good thing," it is not changing. It is getting worse, if anything.

So you really need to understand that people are desperate. We saw this very much with Redux and fen-fen, that the social consequences of losing weight are so significant, there is so much given you when you lose weight, so many more opportunities, that people consider it an investment in their future. They will spend any money that they can. They will take a lot of risk that you won't see people taking risk for in any other disease or condition, an enormous amount of

risk will be taken by people.

It is amazing what people will do. Some of the blogs that they have during Redux and fen-fen, anorexics were telling each other how to get fen-fen and succeeding. It is not so hard to get this stuff when it is out there. That is a part of the problem is that we have a system that really makes it easy for the unscrupulous to prey on us and to cause us harm.

I wanted to talk about some of the specific issues. First is the depression issue. I think the company has done something very good and very smart in including a little depression checklist in the physician's office. But I will tell you right now that, if this gets out to be a real big deal in the public, you can figure out how to answer those questions to get the drug. It is not laser brain surgery. And people will.

So, while that is a nice thing that you have done and, I think, very positive, it is not going to stop anybody who wants this drug. And, as I said, if it seems like there is a real weight

loss to be had, that is going to be everybody.

I have to tell you that I am very upset about it because I have a history of depression and so I can't take this drug, and I was looking forward to trying it because I have a lot of risks that I would assume based on that benefit. So that is a shame.

I think a couple of things; is this an inverse agonist drug or not? I mean, that is kind of basic and I think nothing should happen until that is really figured out because the consequences of it being one or the other is really serious.

I heard one use, or two uses, of the DPP, the Diabetes Prevention Program, Test. I want to make clear that that test didn't separate out the effects of changes in weight loss, diet composition change or exercise. They were all kind of lumped together. So I am not sure that you can really count on anything from that program.

Multiple sclerosis really sends a chill down my back and I will tell you that my partner of 21 years was just diagnosed with multiple

sclerosis. It seems to be more of an art than a science in diagnosing that. It took many months and many, many tests. I am not sure whether they have multiple sclerosis or some other strange demyelating condition specific to this. So that does not feel good. That is not good.

This whole idea of retrograde transmission is really scary. The seizures being dose and duration dependent make it really clear to me that they are related to this drug. When you get out in the public, and you increase the base of people who get this, that is really a problem. I don't like that.

The company once mentioned something about not giving this to people with uncontrolled psychiatric illnesses. I am not sure what they are going to end up doing. So does that mean that people who are on anti-depressants should take this or--I think that that has to be clarified because it seems to me that what mostly they were saying was that, if you have depression, you should not take this. So that is a very big difference there.

As was brought up before, lifetime use for this drug on a two-year trial with not that many people. It is certainly more than other trials have had but, in real life, that is not that many.

That is scary. That is a lot of risk and that is a lot of money. What people are paying in England for this and all over Europe is an extraordinary amount of money.

I have heard a month's supply anywhere from \$175 to \$275. I don't know what it is going to be in this market, but that is a big hit. Most people who are assuming that money for themselves are thinking that you are going to have to just be able to do it for a few months. They are not going to be able to pay that through their lifetime.

I know the insurance reimbursement is something that the company would like, and I would like that too. I don't have the money to invest in it. There is a lot up in the air right now.

I want to make sure that the company makes a very clear postmarketing commitment. We had so much trouble with this with Redux. They made a

commitment verbally and then would not carry through on it. This company does seem to be a lot more responsible but I would really like to hear that they are going to do postmarketing surveillance that is really aggressive.

If you approve this drug, and, frankly, I am glad you don't have to make this decision, but if you choose to approve this drug, even though so much is up in the air, I would say that I would not want it given out to people with a BMI of 27 and comorbidities of blood pressure or cholesterol or abdominal obesity, whatever that means.

Blood pressure, as Sid mentioned, is a tricky issue in fat people. There haven't been a lot of prospective studies on this. People, frankly, have not been able to keep weight off long enough for this to really be well-studied. But, when they have something like the Swedish obesity study, which was actually a surgery study, and people kept off their weight, the blood pressure went down and stayed down for a few years and then went right back up to baseline in spite of the

weight being kept off.

So that says there are some other mechanisms possibly involved, that this is not really weight loss, the change in blood pressure is not that great anyway in this. So I think, particularly under 27, really only diabetes should be an indication.

I, frankly, would be in favor of raising the weight limit to even a BMI of 35 or something like that just to ease into it and the idea was that later on bringing in a little more people at the lower BMI. This is a very scary drug. This is a system we know almost nothing about.

What the FDA has presented so far has really scared me. I lived through Redux and fen-fen and the calls in the middle of the night and the dying people and the people who can't afford the testing they need. Nobody wants to live through that again. I would urge you to keep that in the forefront of your mind.

Finally, I want to thank you for your efforts on our behalf. We are a people who are

much discriminated against and, very often, despised by people including the medical profession. For you to take this time and energy to really try and help us means a lot.

Thank you.

DR. ROSEN: Thank you, Lynn.

Our next speaker is Caroline Apovian. She is representing the Obesity Society.

Caroline Apovian

MS. APOVIAN: Thank you. Good afternoon.

I am Caroline Apovian representing the Obesity Society. We wish to make known that the Obesity Society has received unrestricted financial contributions from Sanofi-Aventis as well as from competing pharmaceutical and non-pharmaceutical companies. The Society is supportive of the development of approval of products for obesity treatment when the safety and efficacy of these products are well supported by rigorous scientific evidence.

In any decision-making about potential approval of obesity agents, this Society believes

the following statements define the context and merit consideration.

The causes of obesity are complex and multi-factorial involving genetic, behavioral and environmental factors that are only partially understood. Obesity is a chronic condition that significantly impairs the quality of life and reduces life expectancy. Obesity increases the risk of heart disease, type 2 diabetes, lipid problems, hypertension, liver disease, sleep apnea and other serious conditions.

Obesity and its related comorbidities, in particular type 2 diabetes, represent one of the major threats to the long-term health and well-being of the U.S. population.

Among obese people, weight loss achieved in the context of medically recommended programs improves quality of life, functionality and reduces the risk of developing future disease. Achievable weight losses as small as 5 to 10 percent of initial body weight appear to be sufficient to confer health benefits in patients at risk.

Currently, treatment options including pharmacotherapies for obesity are limited. With the exception of bariatric surgery, available treatments are associated with modest efficacy and all have side effects that, for some individuals, are intolerable. Additional agents targeted at new mechanisms are very much needed expansions of the treatment armamentarium.

As with people who have type 2 diabetes where lifestyle therapy and adjunctive drug treatment are current standards of care, obese people with health problems deserve similar access to healthcare delivery.

Obesity has long been associated with enormous social stigma. As scientists, we recognize that blame has no role in our discussions. As clinicians, we recognize that persons with obesity deserve our care, our compassion and our health. Obese people deserve access to safe and effective medications that can be reviewed in the same manner as are medications for other chronic conditions.

As clinician, myself, I applaud Dr. Aronne's comments earlier. We applaud the FDA for undertaking a rigorous review of the safety and efficacy data on rimonabant. The clinical and patient community expects the drug-review process to protect them against dangerous and ineffective products. Physicians are eager to have additional tools to help their patients.

We expect that the FDA will review the data on this drug by the same standards it employs for products for other similar conditions and will make its decision as expeditiously as possible.

Thank you for the opportunity to express our views.

DR. ROSEN: Thank you, Caroline.

Preclinical Evaluation of Rimonabant

[Clarification]

DR. ROSEN: We will now move to the lecture component of this. We are going to have Karen come back and just give a brief review of two slides that there was some concern on the committee's part about understanding the toxicity

data relative to the different models.

Then we will move to Dr. Egan's talk.

DR. DAVIS-BRUNO: Thank you. I understand there were a couple of slides that created some confusion and I think the confusion probably started on this one.

[Slide.]

This slide--let me try to explain in a little more detail. This slide is showing convulsions and tremor, various species. But, actually, the data is expressed as the No Observed Adverse Effect Level. What that means is this is the actual dose that the mouse got, the rat got, the monkey got, and does not show convulsions or tremors.

So it is looking at a safety margin relative to the human therapeutic exposure at a 20 mg clinical dose compared to this NOAEL dose in the animal. It is expressed here as a margin of exposure--for example, if the mouse does 20 mg/kg, that exposure compared to the human experience at a 20 mg dose. So, in this case, it is 1 times. It

is at therapeutic exposure.

The rat; the rats got 2.5 mg/kg. It doesn't show convulsions at this dose but that provides less than the clinical exposure in the rat.

Similarly, if you look at the clinical exposure based on Cmax, which is probably the most relevant for looking at convulsions and tremors, you would expect the maximal plasma level to be associated.

What I think created confusion--you can see the safety margin here is expressed as exposures in animals at this No Observed Adverse Effect Level divided by the exposure in humans at this 20 mg clinical dose. I think what created confusion was my last slide with the table.

[Slide.]

It is this one. There is a typo. I apologize for that typo. The typo here is that the therapeutic exposure here, the calculation of the animal exposure, is indicated here as No Observed Adverse Effect Level, NOAEL. That is not true.

This is the animal exposure relative to the clinical exposure so, in this case, these CNS toxicities that we are seeing there.

Does that clarify?

DR. ROSEN: I think so. I would just like to make sure everybody on the committee understands that. I think that was--I think we do understand that. Anybody have any questions or concerns?

DR. DAVIS-BRUNO: I apologize for the confusion.

DR. ROSEN: Paul?

DR. WOOLF: Paul Woolf. Is this the concentration of the drug in the animal divided by the concentration of the drug in humans?

DR. DAVIS-BRUNO: Yes.

DR. WOOLF: At the NOAEL dose.

DR. DAVIS-BRUNO: No. In this case, this is actual incidence that causes the CNS toxicity. The previous slide that I showed you was the no effect level. So we are trying to look at a safety margin in the previous slide. This is showing you the exposures in the animal that cause CNS toxicity

relative to the clinical exposure.

DR. ROSEN: Are you okay with that, Paul?

DR. WOOLF: Is it the concentrations of the drugs in the animals divided by--

DR. DAVIS-BRUNO: Yes; it is based upon exposure. It is based upon pharmacokinetics, not based on the dose in the animal versus the dose in the human. It is exposure.

DR. ROSEN: Right. That is the key, and the PK. Yes. Any other comments or questions from the committee? Thank you, Karen, for your point of clarification.

I would like to introduce Dr. Egan--oh, yes?

LCDR MILLER: Can I just make a comment to the public on Dr. Egan's slides. The handouts that were provided for the public are missing the second half of her presentation. They were not all copied. Those will be available, the full presentation will be available, on the FDA website along with all the other reading material within a week of the meeting.

Thank you.

DR. ROSEN: We, as a committee, people, have those slides, though. It is just the public would have to access them on the website until they are available.

Dr. Egan.

FDA Presentation [Continued]

Clinical Efficacy and Safety of Rimonabant

DR. EGAN: Good afternoon Chairman Rosen and members of the Committee.

[Slide.]

Today, I will be presenting the division's perspective with regard to selective safety issues from this application.

[Slide.]

First, I will briefly summarize the efficacy findings with regard to the weight-management indication. I will then focus on the specific safety concerns that are the focus of this advisory committee, specifically neurological adverse events, seizures, psychiatric adverse events and suicidality so that we may derive

feedback from you as to their meaning and significance.

[Slide.]

Rimonabant was developed under the 1996 FDA guidance for the clinical evaluation of weight-control drugs which stated that, for a weight-loss drug to be considered effective, one of the following criteria must be satisfied; the drug's effect is significantly greater than that of placebo with the mean drug-associated weight loss exceeding mean placebo weight loss by at least 5 percent or the proportion of subjects who reach and maintain a loss of at least 5 percent of their initial body weight is significantly greater in subjects on drug than in those on placebo.

I should point out that the 2007 guidance requires sponsors to meet both criteria.

[Slide.]

Rimonabant satisfied the Division's criteria for efficacy for a weight-loss product. Rimonabant 20 mg once daily along with a hypocaloric diet was shown to reduce body weight by

approximately 5 percent relative to hypocaloric diet alone during one-year trials of more than 6,000 moderately overweight and obese subjects.

As with other obesity drugs, the weight-loss efficacy of rimonabant was attenuated in subjects with type 2 diabetes and, as expected, rimonabant-associated weight loss tended to be accompanied by improvements in levels of triglycerides, HDL cholesterol and hemoglobin A1C in subjects with type 2 diabetes.

[Slide.]

Relative the placebo, rimonabant had no effect of levels of total cholesterol or LDL cholesterol and, for unclear reasons, reductions in systolic and diastolic blood pressure were less than expected given the degree of weight loss.

[Slide.]

But there area important caveats to keep in mind with regard to these efficacy data. First, one must keep in mind the high attrition rates that occurred during the RIO trials. The withdrawal rate during the first year of the four RIO studies

ranged from 32 percent to 49 percent. During the second year, 23 to 58 percent of the re-randomized subjects withdrew and there was no systematic follow up of these dropouts.

But high attrition rates are not unique to rimonabant. They tend to occur with all weight-loss drugs and with some other drugs as well.

[Slide.]

Second, it is important to note that, in the RIO studies, final weight measurements were not obtained on roughly half of the randomized participants due to the high attrition rates. Ignoring data from patients without complete follow up can introduce considerable bias into the analysis.

To account for patients who completed and those who didn't, the last observation on study was used in the statistical analyses. Measuring all participants randomized and conducting an intention-to-treat analysis, using last observation carried forward, is one approach that preserves the

rationale for randomization but it is not the only approach. Each approach has its strengths and weaknesses.

[Slide.]

Third is a concern with the generalizability of the population. The study enrolled predominantly middle-aged caucasian females. Again, this is not unique to rimonabant but was also seen with sibutramine and orlistat. However, statistical analyses showed a significant treatment by age group interaction in both RIO North America and Rio Lipid, the treatment effect being greater in subjects under the age of 65 than in those 65 and older.

Similarly, the treatment by race interaction was significant for RIO North America, Rio Europe and Rio Diabetes. The mean rate change was consistently greater in Caucasians than in blacks and it should be noted that subjects with a history of significant depression were excluded from the trials despite the belief that the prevalence of depression may be greater in the

overweight and obese population.

I will now turn to the safety data.

[Slide.]

This slide depicts the database that was employed in the safety assessment of rimonabant. As you can see, it includes data from a variety of patient populations; schizophrenics, alcoholics, cigarette smokers, in addition to the obese and diabetic subjects consider in the efficacy assessment.

The trial designs were varied as well including different durations, sizes, randomization schemes, drug exposure and drug dosages. For this reason, our analyses often focused on the RIO studies and the studies in diabetics.

[Slide.]

This slide provides a summary of the overall exposure to rimonabant, 20 mg. As you can see, despite the overall large number of participants reported in the database.

Approximately 1600 to date have taken the drug for one year and 441 subjects have taken it for two

years.

I point this out because many of you have expressed a concern about this being a chronic medication, a life-long medication. We are looking at data from 441 patients who have had two years of exposure to date.

[Slide.]

Because of the varied nature of the data and the complexity of the datasets where adverse events were not all located within a single dataset but spread across three datasets, the analyses were difficult especially for safety signals where there were low event rates.

For the purposes of today's analysis, we have focused on the largest of the three datasets, the adverse-event dataset, and for studies where subjects were re-randomized to a different treatment arm, such as 20 mg to placebo. or 5 mg to placebo, we focused only on those subjects who received the same treatment during the entire study.

This was done because of the long

half-life of the drug, about 16 days on average, and the difficulty in assigning the adverse event to a particular treatment arm if it occurred after re-randomization, especially if it occurred during the first 90 days after re-randomization.

I point this out because we know we are losing events by doing this. So you should view our analyses as conservative and an underestimate of the true risks associated with the use of rimonabant.

I will spend a few minutes explaining how the data were analyzed for the specific areas of safety concern, neurological, adverse events including seizure and psychiatric adverse events including suicidality.

But one further comment by way of explanation. Our numbers will differ from the sponsor's as we could only reasonably evaluate completed studies for which clinical-study reports, complete datasets, case-report forms and patient narratives for events of interest had been provided to us. Thus, our cutoff date was December, 2006

and the sponsor's was, in some cases, March of 2007.

[Slide.]

The purpose of the statistical analysis was to estimate the effect of rimonabant versus placebo on safety outcomes. Meta-analyses were performed stratified by study. The studies included were 14 randomized, Phase II and III trials. Per-study sample sizes ranged from 20 to 3,000 per group. The duration of the studies ranged from 4 weeks to 104 weeks.

The primary treatment-group comparison was rimonabant 20 mg versus placebo.

[Slide.]

The primary statistical measures of risk between the two groups were the relative risk, the odds ratio and the risk difference. A few studies had unbalanced randomizations, notably RIO North America and Rio Europe. The meta-analyses were stratified by the individual trials in order to maintain the individual study randomizations and individual study results.

For safety outcomes, with relatively rare events such as seizures and suicidality, an exact meta-analysis and a fixed-effects meta-analysis were performed. For safety outcomes with more common events such as neurological adverse events and psychiatric adverse events, fixed- and random-effects meta-analyses were used.

Data from only the first randomization were included in the primary analysis and sensitivity analyses were conducted that included the additional events from second randomizations.

[Slide.]

One of the deficiencies highlighted in the original review pertain to neurological adverse events. Neurological symptoms including sensory changes, motor impairment and cognitive difficulties appear to have been common in the clinical trials but were not fully characterized. Specific measures were set up to retrospectively obtain and capture neurological symptoms from the 12 completed Phase III studies.

[Slide.]

As a quick reminder, CB1-receptor density is particularly high in the cerebellum, cortex, hippocampus, hypothalamus and basal ganglia, areas of the brain that affect memory, motor function and reward behaviors. They are also present on the peripheral nerves. They play a neuroprotective role in both the central and peripheral nervous systems.

[Slide.]

While the overall rates of neurological adverse events were not terribly different between rimonabant and placebo occurring in 27.4 percent of rimonabant-treated subjects versus 24.4 percent of placebo-treated subjects.

The vast array of these events gave us a considerable sense of uneasiness. The neurological adverse events were not insignificant. They were responsible for 3.5 percent of the discontinuations due to adverse events from the RIO trials among rimonabant subjects versus 1.4 percent of placebo subjects.

These next slides are meant to highlight

this array of different neurological adverse events reported during Georgetown RIO trials. They are grouped according to the areas of concerns; sensory changes, motor impairment and cognitive disorders.

[Slide.]

This first slide summarizes the various preferred terms that were specified by Sanofi in their statistical analysis plan as illustrative of sensory changes. Overall, sensory changes occurred more frequently in rimonabant than in placebo. 14.1 percent versus 9.4 percent.

As you can see, this category was driven predominantly by the adverse event of dizziness which occurred in 8.5 percent of rimonabant subjects versus 5.6 on placebo.

But let me just highlight a few and, by no means, is this a comprehensive list. But you can see paresthesia, hypesthesia, dysesthesia. You have impairments in taste, dysgeusia and, down here, ageusia. You have loss of smell, anosmia, parosmia, and then a whole host of various visual disturbances.

[Slide.]

This slide illustrates the preferred terms for motor impairment. First is specified by Sanofi in their statistical analysis plan and then with additional terms which the division considered to be of significance.

Looking at the sponsor's specified data alone, motor impairment occurred more frequently in rimonabant subjects than in placebo subjects, 1.7 percent versus 0.5. When the other events of interest are added in, those numbers become 3.1 percent versus 1.2 percent.

As you can see, this category was driven predominantly by tremor which occurred in 1 percent of rimonabant and in no placebo subjects. But, again, I point out, dysphonia, aphonia and dysarthria and balance disorder, restless leg, motor dysfunction, clumsiness. Again, this is not a comprehensive list but this gives you a flavor for the array of different neurological events we were seeing.

[Slide.]

This slide highlights the preferred terms of cognitive disorders. Overall, cognitive disorders occurred more frequently in rimonabant than in placebo, 5.4 percent versus 3.3 percent.

As you can see, this category was driven predominantly by amnesia and memory impairment. But, again, the array of symptoms is worrisome; disturbance in attention, lethargy, disorientation, confusional state, cognitive disorder and memory loss.

[Slide.]

This slide provides a forest plot summary of the relative risk of a neurological adverse event which is a composite of all the nervous-system disorders using the updated RIO database. This represents the random effects meta-analysis. As you can see, the combined estimate is 1.7. This was of nominal statistical significance.

What should be noted in this slide as well is the relative risk in RIO Diabetes which was a concern to us because of the neurological

complications of the disease, itself. And, despite improvements in subjects' underlying diabetic condition, they appear to have a slightly higher risk of a neurological adverse event on rimonabant.

[Slide.]

So we looked at the two large studies in diabetic subjects, RIO-Diabetes and SERENADE. SERENADE was a Phase III-B study conducted in treatment-naive type 2 diabetics. This forest plot depicts the relative risk in these two studies.

As you can see, the combined estimate is 3.1. And you can see by the size of this box, which correlates with the precision, really, of the point estimates, that SERENADE added very little to the analysis. But, nonetheless, the risk appears higher in this subpopulation.

So you can see, individually, the numbers of events are small. But, in aggregate, they are worrisome especially given the fact that we don't have follow up or imaging studies on many of these patients.

I am just going to review one of the

patient narratives here as it highlights a concern of ours over the accurate characterization of neurological adverse events. This is a case of a 59-year-old female with no relevant medical history who was enrolled in SERENADE.

The patient was discontinued from the trial due to depressed mood with suicidal ideation on about Day 139. The subject was reported as being recovered from these symptoms seven days later at which time she reported moderate aphasia and moderate vision blurred. These symptoms were reported as not recovered at the end of study which was two months later.

Despite this, no neurological consultation or imaging study was performed. The case-report form indicated that a complementary investigation was performed for this subject which revealed, "no pathological finding." However, no report was in the case-report form. The complementary investigation was apparently an eye exam, although it is unknown if it was performed by an ophthalmologist or a family doctor.

[Slide.]

There is evidence from clinical trials with multiple-sclerosis patients that cannabinoids can reduce the spasms, spasticity or tremor of MS.

Furthermore, results from studies in mouse models of MS suggest that CB1 or CD2 receptor activation by either exogenously administered or endogenously released agonists may oppose the progression of MS by slowing the neurodegenerative process, reducing inflammation and promoting remyelation.

[Slide.]

The number of cases of MS seen in rimonabant trials and postmarketing to date have been small. Two cases of confirmed--and I should mention this is data that we received, this is information that we received, from the company--two cases of confirmed MS occurring in subjects receiving 5 mg of rimonabant in the RIO studies and one case of unconfirmed MS in a subject receiving placebo in the RIO studies.

There were two subjects from the smoking-cessation trials both on 20 mg who had

suspected cases of MS and postmarketing reports received to date include one case of optic neuritis in a subject who had been taking rimonabant for approximately one month and her MRI report suggested MS. One additional case was reported in a woman with a history of MS who had an exacerbation of her MS within five days of starting rimonabant necessitating discontinuation of the drug and hospitalization.

Given the delay in diagnosis that is often seen with MS, and the often non-specific nature of the neurological symptoms and signs with which patients present such as depression, dizziness, vertigo, fatigue, numbness, tingling, visual impairment, weakness, tremor, impaired coordination and balance, coupled with the myriad vague neurological adverse events seen in the rimonabant trials, the lack of investigation of many of these adverse events and the lack of systematic follow up of subjects who discontinued from the trials, the unmasking or exacerbation of MS remains a theoretic possibility albeit one that is biologically

plausible.

[Slide.]

Because of the pre-clinical safety signal for seizure, Sanofi was asked to further evaluate the potential risk of seizures in the rimonabant clinical-trial database by performing string searches on the narratives of all rimonabant studies to identify potential cases of seizure.

[Slide.]

Cannabinoids possess anti-convulsant properties and the endocannabinoid system has been implicated in the regulating seizure threshold, duration and frequency. It is speculated that epileptiform seizure activity elicits an increase in the on-demand synthesis of endocannabinoids resulting in increased activation or pre-synaptic CB1 receptors with subsequent regulation of neuronal hyperexcitability and seizure termination.

[Slide.]

You have heard about the preclinical toxicology data from Dr. Davis-Bruno. But, to summarize, 6 percent of rats and mice and 20

percent of monkeys developed seizures while exposed to doses of rimonabant, 0.5 to 2 times the 20 mg dose versus 1.5 percent of control mice and no control rats or monkeys.

That, in conjunction with the fact that rimonabant accumulates two-fold in the brain with multiple dosing, so AUC:Cmax ratios probably overestimate safety margins in humans, formed the basis for our concerns regarding the seizure potential in humans.

[Slide.]

It should be noted that subjects were excluded from rimonabant trials for the presence of any clinically significant neurological disease, the presence of treated epilepsy or the prolonged administration of neuroleptics within three months prior to screening visits and subjects were discontinued from the trials for the use of neuroleptics.

[Slide.]

In the original submission to the NDA, a total of 7 cases of seizure were reported in the

four RIO trials, 4 on rimonabant 20, 2 on rimonabant 5 and 1 one on placebo. In the updated NDA, 19 cases of seizure have been reported in completed rimonabant clinical trials, 16 of which occurred during the treatment window.

All of these cases were considered in our analyses regardless of the adjudication process. We felt it was important to analyze all of the suspected cases of seizure as the adjudicators were attempting to ascertain retrospectively whether a seizure had occurred but, in many of these cases, no relevant investigations had been performed at the time.

So we weren't convinced that the adjudication process provided any meaningful clarification. Of the 16 cases, 9 occurred on rimonabant 20, 2 on rimonabant 5 and 5 on placebo.

As you can see, the majority of these occurred in the obesity trials.

[Slide.]

This slide presents the person-year analysis of all 16 cases of seizure and then the

person-year analysis of the cases occurring in the obesity studies. As you can see, the incidence rate for seizure in the obesity studies is 2.7 per 1,000 patient years for rimonabant 20 and 0.44 per 1,000 patient years for placebo, a relative risk of 6.1, albeit with a confidence interval of 0.94 to 137.

[Slide.]

In ongoing studies, where randomization is 1 to 1, there have been 8 cases of seizure reported. These include 6 cases on rimonabant 20 and 2 on placebo. The numbers remain small. However, the imbalance between rimonabant and placebo persists.

[Slide.]

Given the known anticonvulsant properties of endocannabinoids and the preclinical finding with rimonabant, and given the 16 cases of seizure which occurred during the trial despite efforts to exclude high-risk patients, as well as the continued imbalance in the occurrence of seizure in ongoing trials, we remain concerned about

rimonabant's potential to increase seizure risk.

Additional clinical experience will clarify this potential risk.

[Slide.]

Psychiatric symptoms, including depression, anxiety and insomnia, occurred frequently during the trials. Many of these symptoms required ongoing treatment with anxiolytics and/or hypnotics. Anti-depressants were also frequently prescribed although their use was grounds for discontinuation from the trial.

[Slide.]

Endocannabinoids are important modulators in pathological conditions such as anxiety, phobias, depression and post-traumatic-stress disorders. CB1 receptors are abundant in the prefrontal cortex of the brain, an area of the brain that is thought to be involved in the regulation of mood, aggression, impulsivity and decision making.

Additionally, CSF levels of the endogenous cannabinoid anandamide correlate inversely with

psychotic symptoms in schizophrenic patients and it
sidewalk believed that anandamide has a protective
role in schizophrenia.

[Slide.]

Therefore, the emergence of psychiatric
symptoms not only depression, anxiety and mood
disorders but also aggression, anger and psychosis
with the use of a cannabinoid receptor antagonist
or inverse agonist is biologically plausible.

There is also reason to believe that
overweight and obese patients may have a
predisposition toward depression. In the
rimonabant studies, subjects were excluded from the
trials for the following: the presence of any
clinically significant psychiatric disease, a
history of severe depression defined as depression
necessitating hospitalization, or a history of two
or more recurrent episodes of depression, or a
history of suicide attempts or the prolonged
administration--I'm sorry; that should be bulleted
over. That was actually a different exclusion
criterion--but the prolonged administration of

anti-depressants within 3 months prior to screening.

Furthermore, they were discontinued from the study if they were started on an anti-depressant. A total of 11,225 patients were screened in the RIO studies. A total of 113, or just 1 percent, failed screening due to these exclusion criteria.

[Slide.]

Despite these exclusion criteria, the medical histories of subjects who were enrolled in the RIO studies revealed that a significant number of them had an underlying medical history of depressed mood disorders and disturbances. This slide depicts the breakdown by study. The pooled analysis revealed that the baseline history of depression was slightly higher in the rimonabant 20 group at 7 percent versus placebo at 6 percent.

However, I would point out that only 1.4 percent on rimonabant 20 versus 1.1 percent on placebo reported their depressive symptoms as ongoing and trial entry.

[Slide.]

This slide indicates the terms that were used to evaluate the psychiatric profile of rimonabant. This is the standard approach to recording adverse-event data from clinical trials and it is based on the Medical Dictionary for Regulatory Activities, or MedDRA.

Terms under the Primary System)rgan class, or SOC, psychiatric disorders, under the high-level group terms and then under preferred terms. The high-level group terms that we focused on were anxiety disorders and symptoms which include such preferred terms as anxiety, nervousness, stress and tension, depressed mood disorders and disturbances which included depression, depressed mood, anhedonia and dysthymic disorder, sleep disorders and disturbances which include insomnia, parasomnia, and somnolence--again, this is just a brief listing--and mood disorders and disturbances which include affect alteration, crying and mood altered.

[Slide.]

Overall, subjects in the rimonabant 20 mg group were more likely to experience a psychiatric adverse event than those on placebo. In the pooled RIO studies, in subjects receiving the same treatment during the entire study, 26 percent of rimonabant's treated subjects versus 14 percent on placebo experienced a psychiatric symptom reported as an adverse event.

Again, because we don't include events occurring in subjects who were re-randomized during a second randomization to a different treatment arm and because we have confined our analyses to the one adverse-event dataset, this should be viewed as an underestimate.

The incidences of psychiatric adverse events in all of the high-level group terms were higher for rimonabant than for placebo; anxiety disorders at 11 percent versus 5 percent, depressed mood at 9 percent versus 5 percent, sleep disorders, 8 percent versus 4 percent and mood disorders and disturbances 3 percent versus 0.8.

An overriding theme is the almost 2 to 1

imbalance that seems to occur repeatedly.

[Slide.]

Here we are looking the relative risk of experiencing a psychiatric adverse event in the RIO studies. Again, this is a composite of all of the preferred terms. The relative risk, using the random effects model, was 1.9. This was of nominal statistical significance.

[Slide.]

We then performed some additional analyses looking at the relative risk of a psychiatric adverse event by age, gender, geographical location and degree of weight loss. It appears that the risk may be higher in the 65 and older age group relative to the under 65 with relative risk of 3.1 and 1.7 respectively.

There was no difference in relative risk between U.S. and non-U.S. participants, 1.7 and 1.8.

[Slide.]

With respect to gender, the relative risk trended slightly higher for males than females, 2.1

versus 1.7. Because of a possible association between weight loss, itself, and symptoms of anxiety and depression, we looked at the relative risk in 5 percent weight-loss responders versus non-responders. As you can see, the relative risk was really no different regardless of the weight-loss response, at least when defined by a 5 percent cutoff.

[Slide.]

Because there was a relatively large number of subjects who were enrolled in the RIO trials with a baseline medical history of depressed mood disorders and disturbances, we decided to look at those individuals relative to the larger group to see how many of that went on to have a psychiatric adverse event during the trial expecting, of course, that having a baseline history of depression would increase their risk of experiencing such an event.

And, indeed it did. The incidence of a psychiatric adverse event in subjects who had a baseline history of depression was 32.2 versus 17.6

among patients who did not have a baseline history of depression. But keep in mind that subjects with more severe forms of depressed mood disorders were excluded from the trials and also bear in mind that this also indicates that roughly 88 percent of subjects who experienced a psychiatric adverse event did not have a baseline history of depressed mood disorder and disturbances.

This is in contrast to what the company has told you that having a baseline history of depressed mood is predictive for who will have difficulties with rimonabant.

[Slide.]

These psychiatric adverse events, in general, more often necessitated discontinuation of study drug. Psychiatric adverse events accounted for 8.5 percent of the discontinuation from the study among subjects on rimonabant versus 3 percent of placebo subjects. Most subjects were reported as recovered or recovering from their psychiatric adverse events at study end. However, subjects were reported as recovered even if their symptoms

resolved because of treatment with an anxiolytic or hypnotic or anti-depressant.

Here you see that 8.5 percent of rimonabant subjects who were enrolled--and this is the whole group--8.5 percent of people who were enrolled in the RIO studies on rimonabant 20 mg required the institution of an anxiolytic or hypnotic during the trial versus 4.1 percent of those on placebo.

Another 4.8 percent of subjects required institution of an anti-depressant versus 2.9 percent of those on placebo. These numbers are felt to be an underestimate because some subjects were placed on a beta-blocker for their anxiety symptoms. Our review of the patient narratives and case-report forms reveals still others whose treatments were simply not recorded in the datasets.

[Slide.]

Our conclusion was that rimonabant 20 mg was associated with an approximate doubling of the risk of a psychiatric adverse event and a roughly

three-fold increase in discontinuation from the trials due to these events. These events included predominantly anxiety disorders and symptoms, depressed mood disorders and disturbances and sleep disorders and disturbances.

This was from trial data in subjects in whom major psychiatric disorders had been excluded.

What remains unknown is what the experience with rimonabant will be in a less highly screened and potentially more depressed patient population.

[Slide.]

In the original NDA submission, one case of suicidal ideation in a subject on placebo was reported. Initially review of the patient narrative and case-report forms by the medical reviewer revealed several other cases which had not been reported. It was at that time that Sanofi was initially asked to reassess the database to investigate for other cases of suicidality.

Then, subsequently, the division also requested that Sanofi obtain a formal assessment of suicidality from Dr. Kelly Posner's group at

Columbia University. You were introduced to Dr. Posner's methodology earlier today.

[Slide.]

This slide again reviews the various categories of interest within the Columbia classification system. These categories break down into definitely suicidal, categories 1, 2, 3 and 4, or possible suicidal, Columbia categories 5, 6 and 9.

[Slide.]

A total of 1201 patient narratives were prepared by Sanofi and submitted to Dr. Posner's group for a blinded analysis. The analysis identified 91 cases of either definitely or possibly suicidal. This included five cases which occurred on haloperidol active treatment.

The majority of cases were assigned to Columbia category 4 which is suicidal ideation. Of the 91 cases, 64 were considered to be suicidal ideation. This included 14 cases occurring on placebo, 10 on rimonabant 5 and 40 on rimonabant 20.

Now I would like to take a couple of minutes to explain the methodology employed by our statisticians in the selection of studies to be used in the analysis of suicidality.

[Slide.]

A total of 13 studies were used in our analyses, RIO North America and EFC 4796, which was a large smoking-cessation trial, re-randomized patients during a maintenance phase after the randomized treatment. Only data from the first randomization was used in the primary analysis.

The control group employed for study EFC 4796 was rimonabant 5 mg as there was no placebo group in the first randomization. Sensitivity analyses were performed both including all suicidality events and ignoring the second randomization as well as excluding studies with a second randomization.

[Slide.]

Thus, the total number of suicidality cases contributing to the analyses is 74, 46 on rimonabant 20 which included: four suicide

attempts, 39 suicidal ideations and 3 not enough information, non fatal; 8 cases of suicidality on rimonabant 5 mg, 1 preparatory act toward imminent suicide, 6 suicidal ideations and 1 not enough information, fatal; and 20 cases on placebo, 7 suicide attempts which, I should point out, 3 occurred in the schizophrenic trials and 3 in the alcoholic trials and 1 in the smoking-cessation trial and 13 cases of suicidal ideation.

[Slide.]

This slide illustrates the results of the fixed effects meta-analysis. Again, I remind you that, in the smoking-cessation trial. EFC 4796, that we have used the 5 mg group as the control group because there was no placebo group in the first randomization.

As you can see, by this very small point estimate, it really adds little to the composite analysis but, nonetheless, I point that out.

The odds ratio for the incidence of suicidality, rimonabant 20 versus placebo for all of the studies contributing to the analysis is 1.9

which is of nominal statistical significance.

[Slide.]

Here we are looking just at the 7 obesity studies so you can forget about that smoking-cessation and whether or not we should have used 5 mg as our control arm. You can see our point estimate has changed very little, still 1.8.

I should point out that sensitivity analysis, adding the second randomization events to the first randomization, resulted in an exact text odds ratio of 1.93.

[Slide.]

To date, four completed suicides have been reported, 3 in the entire rimonabant clinical-trial database and one postmarketing. All of the cases of suicide occurring during rimonabant clinical trials have occurred in subjects on active treatment, none on placebo.

To briefly summarize these cases: in RIO North America, a 63-year-old gentleman taking rimonabant 5 mg; in STRADIVARIUS, which is an ongoing study; a 36-year-old male on rimonabant 20

mg; and, in CRESCENDO, a 77-year-old male on rimonabant 20 mg. I know that the sponsor highlighted this as a case where the gentleman had stopped rimonabant a week before he committed suicide. Just to clarify that, that is absolutely true and the reason he stopped it is that the IRB at that investigation site insisted that a letter be circulated warning of the risk between rimonabant and suicidality; postmarketing, a 33-year-old male on rimonabant 20. Again, the details on this case are sketchy but we do know that this gentleman had a BMI of less than 20.

[Slide.]

But even if you believe that there is an association between rimonabant and suicidality, what is the nature of that association? Was ascertainment bias a factor? Ascertainment bias is generally a concern when doing epidemiological studies but this concept has been suggested in the association between anti-depressant use and suicidality in adolescents and young adults.

Depressed individuals who are placed on an

anti-depressant become activated and are more apt to vocalize their suicidal thoughts or subjects whose social anxiety is effectively treated with an anti-depressant may exhibit increased verbalization and communication with others.

But depressed patients were specifically screened out of the rimonabant trials--and for a reason, I might add. And rimonabant is not an anti-depressant.

[Slide.]

Is it that patients who report common drug-related adverse events may be questioned more about other adverse events compared with placebo patients?

For example, as was recently suggested in an editorial in the New England Journal of Medicine, the increased reporting of sexual dysfunction in depressed patients taking an anti-depressant might lead to further questions about other adverse events and possibly increase the odds of reporting suicidal symptoms.

But the most common adverse event in

rimonabant-treated patients is nausea. Would increased reporting of nausea in a population of non-depressed patients on rimonabant lead to increased reporting of suicidal symptoms? And, besides, depressive and anxiety events were reported, on average, two months later than nausea events.

[Slide.]

Were rimonabant-treated subjects more apt to make more unscheduled visits, again, due to other side effects of the drug such as nausea, and voice other side effects at those visits? But the mean and median number of study visits were the same for both the placebo and the rimonabant groups and the dataset which contained unscheduled visits such as the clinical laboratory datasets were all reviewed and did not reveal any disproportionality between treatment groups and the number of unscheduled visits.

[Slide.]

Ascertainment bias was an interesting hypothesis. If you believe that this explains the

increased rate of suicidality in rimonabant subjects, you must assume that it is operative in 9 of 13 studies and it explains odds ratios varying in magnitude from 1.4 to 16.7. You must also assume that there is an equal background rate of depression in placebo and rimonabant subjects as suicidality is a symptom of depression.

But, as you recall, the rates for depressed mood-disorder adverse events were 9 percent in rimonabant subjects and 5 percent in placebo subjects.

For those who would say that, perhaps, ascertainment bias explains the higher reporting rates for depressed mood disorders, I point out that a larger percentage of patients treated with rimonabant discontinued early from the trials due to depressive disorders and a larger percentage of rimonabant subjects required anti-depressant therapy.

These outcomes, perhaps more indicative of more severe forms of depression would, I believe, be less susceptible to ascertainment bias.

[Slide.]

Or is it the weight loss, itself, and not the drug that is prompting the suicidal ideation, the so-called semi-starvation neurosis? Subjects who experience significant weight loss may exhibit psychiatric disorders such as depression, anxiety and suicidal ideation.

[Slide.]

We explored that possibility here. This slide looks at the weight change from baseline in suicidality subjects, indicated by the blue circles, relative to the mean weight change in subjects who did not experience suicidality, indicated by the yellow lines. The red lines indicate 1 standard deviation above and below the mean.

If, indeed, the weight loss was the cause of the suicidality signal, we would have expected to see more of these circles concentrated down in this area. But, if anything, they are concentrated around the mean and above the mean. So we don't believe that these data support that hypothesis.

[Slide.]

Is the association due to chance? You can never rule out chance but, again, is it chance in 9 of 13 studies?

[Slide.]

Or is the association causal? And we strongly believe that it is causal. We know that it is biologically plausible given the role of the endocannabinoid system specifically the CB1 receptor function in the central nervous system. After all, that is why the sponsor excluded depressed patients.

We find a similar increase in the risk of depression in the clinical trials and suicidality is a symptom of depression. So it is not really surprising. In fact, it would have been more surprising if we didn't see it.

[Slide.]

So, in summary, our meta-analysis indicates an increased risk for suicidality, specifically suicidal ideation, in subjects taking rimonabant 20 mg versus placebo. There is an

increase in relative risk of 80 to 100 percent and an increase in absolute risk of 0.3 percent.

This correlates with one additional case of suicidality per year for every 300 patients treated. And these estimates may be low, given the higher percentage of rimonabant-treated patients who drop out of the study due to psychiatric adverse events.

[Slide.]

Rimonabant is currently approved in 30, I guess now 37, countries. As of March 1st, 2007, an estimated 100,000 people, mostly from the United Kingdom and Germany, have been prescribed rimonabant. The top ten preferred terms reported to the European regulatory authorities to date are; depression, nausea, depressed mood, anxiety, fatigue, dizziness, sleep disorder, suicidal ideation, agitation and asthenia, not surprising given what was observed in the clinical trials.

I am just going to ask Dr. Eric Colman to come up for a minute. He is going to explain some of the data that we have received from the EMEA.

[Slide.]

DR. COLMAN: These are data that we just obtained within the last week and, in some cases, actually yesterday. But I think it is important to show the folks these data. This is one advantage of not approving a drug too soon because the Europeans approved it first. So we can go to them now and ask for their experience after they approved it and get a better sense what is going on.

But, what we wanted to do was look and see what rimonabant looked like compared to the two other weight-loss drugs that had been around for 7 or 8 years. So, we focused on that. But what this shows you, and I will just remind you that rimonabant, the approval began around this time last year. Sibutramine was approved in Europe in 1990, and orlistat was approved in 1998 in Europe.

So, this is from the same database, the numbers you are looking at, and these are cumulative since the dates of approval. What you see here are the total adverse events for any

event, anybody's system. These are the total number of cases that were spontaneously sent to the system.

So, for rimonabant, you have 384 cases. Sibutramine, you have 567, and orlistat, you have 2,734. Orlistat clearly is used more than sibutramine in Europe, and I believe that is true in this country, as well.

So, those are the total number of all adverse events in this data system.

Now, this column shows you the number of psych-related adverse events for these various drugs. And, again rimonabant over the course of about a year, there are 208 psych adverse event cases, sibutramine 117 and orlistat 208.

So, you can see a function of the total number of AEs, the psych Aes for rimonabant make up 54 percent of the total adverse events in this system. That compares with 21 percent with sibutramine, and it is not surprising. As we discussed earlier, sibutramine is an antidepressant-like in terms of its pharmacodynamic

action. It is centrally active agent.

Orlistat, which is really not absorbed into the system, you wouldn't expect any real psychiatric effect, at least direct psychiatric effect, and that only makes up 8 percent.

So, clearly, within one year, over half of all the adverse events are being contributed to by psych-related adverse events.

[Slide.]

Again, these are data from the EMEA, postmarketing data spontaneously reported. We wanted to know how many cases of suicidal ideation the EMEA had for these compounds. Again, orlistat has been on the market over there since 1998. They have 14 cases of suicidal ideation.

Sibutramine has been on the market in Europe since 1999. They have 15 cases of suicidal ideation. Rimonabant has not even been on the market for one year, almost one year, and they have 27 cases of suicidal ideation.

[Slide.]

DR. EGAN: It is interesting to look at

this number because this is about what we would have predicted based on our absolute risk.

To our way of thinking, the risk-benefit analysis sorts out this way. Rimonabant is effective at reducing body weight and rimonabant associated weight loss does improve triglycerides, HDL cholesterol, and hemoglobin A1C and fasting insulin levels, and there are probably benefits that are yet to be identified.

The risks associated with the use of rimonabant include an approximate doubling in the risk of psychiatric adverse events specifically depression, anxiety, insomnia, and mood disturbances, an approximate doubling in the risk of suicidality, specifically, suicidal ideation, an increase in a constellation of neurological adverse events of unclear significance, a possible increase in seizure risk, an increase in nausea and vomiting--which we haven't really discussed today although it is the most commonly reported adverse events, and many of these risks appear more pronounced in diabetics--and as yet to be

identified risks, and there will be further risks.

Our knowledge of the endocannabinoid system is still evolving and there is a lot more to be learned, but keep in mind the signals we are seeing are in a relatively small and highly select population, carefully screened and receiving drug in a controlled setting.

The potential market for this drug and our continued uncertainty about its risks, both known and unknown, lead to our concern about the use of this drug in the general population.

Weight loss may have benefits in and of itself. However, the effect of drug-associated weight loss on cardiovascular morbidity and mortality remains unproven. The results of studies, such as the Women's Health Initiative, highlight a concern with continued reliance on surrogate endpoints that ultimately do not achieve the desired goal of reducing cardiovascular morbidity and mortality.

In that regard, rimonabant's lack of effect on LDL cholesterol or blood pressure is

certainly notable.

[Slide.]

I would just like to briefly mention an ongoing clinical outcome trial that Sanofi is conducting. It is called CRESCENDO for Comprehensive Rimnabant Evaluation Study of Cardiovascular Endpoints and Outcomes. 17,000 abdominally obese patients at risk for cardiovascular disease are to be enrolled. The study is 50 months in duration. The primary outcome is myocardial infarction, stroke, or cardiovascular death. The study is scheduled to be completed in January of 2010. This may answer the question of whether the improvements observed in these surrogate endpoints are clinically relevant.

[Slide.]

I just wanted to take a moment to acknowledge all the members of our review team for their tireless efforts in this review process.

[Slide.]

We have prepared the following three questions for your discussion and input. I can

review them, unless you want to take questions now.

DR. ROSEN: I think we should just take questions for you first, Dr. Egan. Thank you for an eloquent presentation.

DR. KREISBERG: Dr. Egan, that was a spectacular analysis. In all of the studies that were used for the determination of adverse effects, it is remarkable that men are underrepresented. They represent 30 percent. Yet, all of the completed suicides were in men.

Do you think that the composition of the study group underestimates the risk of suicidality?

DR. EGAN: I guess that is a possibility. If you looked at the studies that were a little bit more gender balanced, such as RIO-lipids or RIO-diabetes, in real lipids it is interesting. We often saw an increase in almost every type of adverse events, and whether that was because of the gender imbalance I am not sure. We did not do a separate analysis by gender for that study alone.

DR. ROSEN: Dr. Gilman and then Dr. Wang and then Dr. Woolf.

DR. GILMAN: I have a series of questions. I hope you will bear with me for just a moment or two.

I thought it very frustrating to go through the material, both the FDA material and the material from the sponsor, because there was a lack of specificity, so let me see if you have any--or the sponsor has any--answer to this series of questions.

First, the symptom of dizziness. Dizziness is a terrible symptom because a physician, a neurologist, never knows what a patient means when the patients complains of dizziness. It can mean lack of balance when walking, of a sense of vertigo--that is, a spinning of the environment.

It can mean nausea. It can mean loss of vision. It can mean weakness in the legs. It can mean sweating. In other words, dizziness is a non-descriptor of what the patient is perceiving, so you have to drill down and find out what exactly the patient is experiencing.

I found nothing in here to explain this further except an occasional mention of vertigo, which means a spinning of the environment or of the person.

Do you have any more information, or does the sponsor?

DR. EGAN: Probably the sponsor could clarify this better. The basic methodology for assigning terminology to these adverse events is to take the verbatim term, which then gets translated through several different layers. So it goes from there to an actual adverse-event term, to a preferred term, to a high-level term, to a high-level group term, to a primary system organ class.

So, you are right, a lot can be lost in the translation. And we also had a problem with language where angina was often reported, but it was frequently to describe sore throat instead of the angina that we are more familiar with.

So, it was a confusing process, because, yes, it is not unique to Sanofi. It is a difficult

problem.

DR. ROSEN: We might ask the sponsor if they have some additional data for just a brief response.

DR. BRADLEY: My name is Walter Bradley. I am Professor of Neurology at the University of Miami. I have some conflicts; that is, my time is compensated for the department by the sponsor, and I receive reimbursement for my travels.

I have looked at a fair number, but not all of them, of the case-report forms and other information of that nature that has dizziness and, as you well know, it covers all sorts of different disorders. There are a number. True benign positional vertigo. There is one of Meniere's disease. But the vast majority of them are uncategorized and it is impossible to know what they are.

DR. ROSEN: Thank you very much.

You can finish your line of questioning and then we can move on.

DR. GILMAN: Yes, please. The second

question has to do with the tremor. Once again, the word tremor doesn't mean a great deal without more description. For example, cerebellar disease causes a proximal tremor so that there is a tremor on reaching certain other disorders, such as central tremor called a distal tremor, tremor at rest usually is associated with Parkinson's disease, tremor on action may be anxiety-related.

So, the word tremor by itself is only a teaser. It doesn't tell you what is going on. Do you have any more information about that?

DR. EGAN: Again, we were just using the preferred terms that were assigned by the sponsor, so I can't tell you the methodology that they used to assign those terms. But I am sure they can.

DR. ROSEN: A brief comment from the sponsor?

DR. BRADLEY: Again, I have looked at a fair number of those. We looked particularly at cases that were unilateral because of the possibility that those were parkinsonism, and the majority of those, in fact, although classified

under tremor--the terms used were actually jerking of the limb, not actually tremor--although it fell under the rubric of tremor when classified according to the standard methods.

There were whole body tremors. They were bilateral tremors, and it did not again appear to be specific. I could not get the sense that this was benign essential tremor that was being activated.

We did look specifically to see whether there was any association with anxiety, and, in fact, there was no tying up between the cases that had anxiety or tremor and vice versa.

DR. ROSEN: Thank you for that clarification.

DR. GILMAN: I won't go on too much longer.

Under "cognitive disorders," there were many terms including amnesia, memory impairment, disturbance in attention, et cetera, et cetera, lethargy, syncope.

Were there any objective measurements

made? Did anybody do a Mini-Mental State examination so they would have some sort of measurement of what exactly this meant, or is this only a symptom that a physician or an individual on the site recorded?

DR. EGAN: That's correct. This would have been recorded by the investigator at the investigator site. Now, one of our concerns was, yes, we actually--if you type up a table with all of the neurologic adverse events that were listed by preferred term, it encompasses 3 pages.

So, that is why we said we had a great deal of difficulty getting a grasp on what they all meant, because so many different terms were used. Part of this may have been because that is how the patients were reporting it. It may have been just difference in investigators.

A lot of these people did not have neurological consultations, did not have any kind of complementary investigation, so getting a firmer diagnosis is difficult.

DR. ROSEN: One of the issues of querying

with adverse events is that you have these broad terms which are difficult and require further investigation.

DR. GILMAN: I appreciate that. However, there is no substitute under those circumstances for doing an objective test, and then you would know what you are dealing with.

For example, Mini-Mental State exam can be done in five minutes or so, and you get a number. So you know what you are dealing with. The patient may have the symptoms but be cognitively intact. We just don't know from this data set.

Thanks. I am through.

DR. ROSEN: Dr. Wang.

DR. WANG: You showed us your data on possible effect modification of the risk for adverse psychiatric events by age, gender, and weight loss.

Do you have similar data on how the relative risks might vary by baseline BMI?

DR. EGAN: Yes. I mean we--are you talking about a psychiatric adverse event like

baseline BMI?

DR. WANG: Yes.

DR. EGAN: I think we did do that analysis and I am sorry--I am not sure if Todd or Lee remember the--I mean you are right because, typically, people in the higher BMI categories, a BMI of over 40, tend to have more depression.

I know from the sponsor's analysis they said that that was not found. But we will get back and get that information to you. We did it for suicidality, but that's, you know--

DR. WANG: It is pertinent also because I think, you know, in your briefing material you sent us, it looked like there was also a suggestion that there was greater efficacy.

DR. EGAN: Efficacy in that group.

DR. WANG: So, that would change the risk-benefit profile, but anyway, that would be helpful.

DR. WOOLF: This series of studies were done under the FDA guidance of September '96. They met the criteria for weight loss, but there was

another criteria that they did not meet, and that is--and I am quoting from the memo of 9-24-96 that said, in order to obtain an adequate estimate of the safety of weight control drugs for long-term administration, generally, about 1,500 subjects are expected to complete 12 months with 2- to 500 of these completing 24 months.

According to the adjudicated data that we received a couple days ago, only 975 patients, in fact, completed the 20 mg dose. In the unadjudicated data, I think there were two less. So, in point of fact, it appears that only two-thirds of required patients, by FDA guidance, this is what it says in the data received from the FDA.

Actually, we completed the full year and I would like to know whether obviously that is correct, because I think that has a huge impact on whether we can proceed or not.

DR. EGAN: I think the number was actually closer to 1,100 who finished approximately 12 months of treatment on rimonabant 20.

DR. ROSEN: Comments from the sponsor?

DR. DURRLEMAN: Yes, maybe two points of clarification that came up earlier today concerning the gender difference in the risk for suicidality or depression.

We have performed this analysis and, as presented in the briefing package of the FDA, we noticed that the risk for men is 1, basically. So, really the increase in symptoms of suicidal thoughts is mainly toward women as presented in the FDA briefing package.

We also have performed the analysis of risk for psychiatric symptoms and suicidality for BMI categories, and, in fact, as we go to higher BMI class, the risk is smaller and smaller. As far as the duration is concerned, in our original NDA, we had the numbers as presented. We have a number of ongoing studies that we are going to propose and present for the duration of exposure.

DR. ROSEN: Can we just clarify the number again? I am not sure we have clarification on the completion, the number completed and adjudicated

for one year.

DR. GURAL: Total patient exposure for one year at 20.

[Slide.]

As you can see in this slide, and I will point, 20 mg exposure up to one year, it is 1,134, two years of exposure, 441. In the smokers, which is an additional population, although not intended for the indication, there is an additional 183.

DR. WOOLF: There is a 300-patient discrepancy here, or 200-patient discrepancy between the data that you were telling us here and that the FDA analyzed.

DR. ROSEN: Is that from the completion, from what we have December 2006 to March of 07?

DR. GURAL: I am sorry, could you repeat your question?

DR. WOOLF: The document that we received a couple days ago from the FDA had 975 patients completing the RIO studies on the 20 mg dose out of a total of 2176, and yet you have got 250 patients more, so were they included in the data set that

the FDA was able to analyze, or where did they come from?

DR. GURAL: These are from the completed four RIO studies as identified here in the footnote.

We will validate the number for you.

DR. CIRAULO: I will try to get several questions in. Let me just say I am worried about the use of this drug in a population that has not been discussed today, and that's the schizophrenic populations who develop metabolic syndrome from atypical antipsychotics.

I am especially concerned because I didn't hear much about the schizophrenia study although it was in some of the background material. So I just want to throw that out there.

I am also concerned that some of the anxiety symptoms--and they were talking about suicidality--but some of the anxiety symptoms may indeed be psychotic panic especially, as you pointed out, the role of the system, the cannabinoid system and anandamide, in reducing

psychosis.

So, I am wondering about how carefully--the comments made earlier--how carefully those were queried, how skilled the people who were making those queries about psychological symptoms were.

So, I think that my general feeling is I would agree that there is an underestimation of the severity of the psychiatric risk associated with this drug.

DR. ROSEN: Any comments from Dr. Egan?

DR. EGAN: Yes, I was just looking for a slide that we do have. We do have a slide prepared on the psychotic and dissociative events that occurred, which you are right, they are--we didn't discuss this, but we are concerned about evidence of psychosis, and you can see the imbalance here where 2.7 percent of rimonabant users versus 0.5 percent of placebo--and this is just the RIO study, so we haven't factored in the schizophrenics--experience a dissociative or psychotic disorder, and we had 1 percent developed

aggression.

So, yes, you are right. One of the populations we do have tremendous concerns with are the patients on atypical antipsychotics who tend to gain a lot of weight and would likely seek out a drug like this.

DR. ROSEN: Dr. Carpenter.

DR. CARPENTER: A question regarding the European data, which I think is very helpful in terms of seeing an experience in current practice, and that is, do we have any sense of the denominator? Do we know roughly how many scripts of each of those compounds have been written since approval or since marketing?

DR. COLMAN: No, I don't have that specific data for the other two compounds. Roughly 100,000 have been written for rimonabant. We do have something called--and I hesitate a bit to mention it--it is called data mining, which does take into account the use of the various drugs. And what I can tell you is the signal for suicidal ideation is about 2 1/2 fold higher for rimonabant

versus sibutramine, and that does take into account the extent of use. So, that is about the best I can give you right now.

DR. ROSEN: Michael, did you have a question?

DR. PROSCHAN: Yes. A lot of this suicidality discussion seemed to hinge on--well, some of it hinged on that smoking study 4796. I was just looking at your slide 49 where it shows that smoking trial with kind of a big confidence interval. We can't actually see how big it is because it keeps going. And yet that trial had very large sample sizes and the total number of events was fairly high. And so I would expect that confidence interval to be narrower than it is and it doesn't seem to match figure 7 in document you sent us although I just realized, as I was looking at this, that 7 is actually risk difference rather than the odds ratio.

Is that the correct length of that confidence interval?

DR. EGAN: Yes. I can probably sort out

and find the exact confidence interval for you and, actually, this is interesting in and of itself. And she chose 5 mg here thinking it was more or less giving something away, because we expected to see some events on active treatment, and we were willing to concede that in order to put that in the analysis. So it wasn't done to deceive anyone. We thought we were actually helping the sponsor and doing a very conservative analysis.

DR. PROSCHAN: Yes, that was interesting because earlier the sponsor objected to that use of it, use of the 5 mg, because it is an active dose.

But, like you said, you would expect that to make it look even, you know--

DR. EGAN: Better for them.

DR. PROSCHAN: Yeah, less of a problem.

DR. ROSEN: Dr. Egan, if you remove that one study, do the confidence intervals go to 1 with the removal of the smoking study?

DR. EGAN: I did mention the sensitivity analysis. It is not included obviously in the obesity study. I think I mentioned it was 1.93.

Sensitivity analysis first ignoring the second randomization revealed an odds ratio of 1.7. That confidence interval was 1.0 to 2.8, p-value of 0.0283. And then excluding the studies with a second randomization, the odds ratio is 1.6 with a confidence interval of 0.89 to 3.03 and a p-value of 0.1077.

DR. ROSEN: Thank you.

Any other questions from the Committee?

Dr. Burman first, and then Dr. Gilman.

DR. BURMAN: I would like to focus on the question of whether psychiatric-disease screening, a history of psychiatric disease, can be used to predict who is going to get future psychiatric problems from rimonabant.

It seems, if I understood correctly, that there is a discordance between the sponsor's result on this and your results, but I don't know that I understand why there is such a discrepancy.

Do you have a possible explanation?

DR. EGAN: I think that they limited their analysis to depressed mood disorders and

disturbances. What we looked at were people who had a baseline history of depressed mood disorders and disturbances, and then looked at the number of people from that group who developed a psychiatric adverse event. Again, that was a composite. It wasn't just that they went on to develop depressed mood. They went on to develop a psychiatric adverse event.

What we found was 32 percent of those with a baseline history went on to develop a psychiatric adverse event, and only 17.6 percent of those who did not have a baseline history of depression went on to develop a psychiatric adverse event.

But if you looked at the total number of psychiatric adverse events, I believe there were 1,235 of them, all but 153 of them occurred in subjects who did not have a baseline history of depressed mood disorder.

DR. GILMAN: Let me ask you about seizures now. I would like to cycle back to that again. On the FDA's page 41 and on the sponsor's page 99, this is taken up and I just wanted to ask you about

the type of seizure, because it is not clear here.

As I make out this table, there are three patients on placebo who had seizures and eight that were on drug that had seizures.

I know there have been two experts who have adjudicated these case report forms and concluded these are seizures, but that does not satisfy me much. I wonder if there is any descriptor that would help us understand what is going on. Is there a specific kind of seizure? Is it psychomotor?

DR. EGAN: It was all--it could have been a petit mal. It could have been a focal motor. It was not limited to grand mal.

DR. GILMAN: The problem with petit mal, it's a disorder of children, and when people say they have petit mal, they probably mean it's a partial complex seizure. Petit mal is a very specific entity seen in children, not adults generally unless they have had it from childhood.

I am troubled by this table. I don't think the data here are very good as reported, at

least by other than sponsor or the FDA.

DR. ROSEN: We have a brief sponsor clarification.

DR. GURAL: We have with us Dr. Mattson, who did do the blinded evaluation of all the potential cases for seizure. Dr. Mattson.

DR. MATTSON: Thank you.

I have the same conflict as Dr. Bradley. I am here on behalf of the company, the sponsor.

In response to the kind of seizures, most of them were convulsive that we considered likely seizures, and the basis for that diagnosis was the usual things like tongue biting, mouth biting, incontinence, and reported convulsive movement.

There were a few in whom they could have been complex partial seizures or they could have been a dissociative episode. We considered those possible and included them as being seizures.

There were about a quarter that did not conform to what one would consider a description of an epileptic seizure as is very common in people with a diagnosis of seizure coming to an epilepsy

center. About a quarter of them are not epilepsy.

But most of them were convulsive as you would expect in an adult population. In children or in the elderly, we often have partial presentation. So, most of them were convulsive.

DR. ROSEN: Thank you.

DR. EGAN: Your concern is a valid one. This was a retrospective analysis and there often wasn't very much information that was recorded.

DR. ROSEN: Dr. Hirsch.

DR. HIRSCH: I don't know who to ask the question. We hear a lot about the smokers and their adverse effects. I just want one or two other questions about the group. I gather they didn't stop smoking, apparently, but without giving details of that, I do wonder did they lose weight.

DR. EGAN: I don't know that. I don't even know if it was measured, I honestly don't know.

DR. HIRSCH: I wonder whether the ones who did stop smoking gained weight. I would be interested in knowing anything you can easily tell

us about it.

DR. ROSEN: Briefly.

DR. SEBILLE: Marie Sebille, Clinical Development, Psychiatry, Sanofi-Aventis.

We have investigated the efficacy of rimonabant in smoking cessation. You have seen the program we have conducted with three short-term studies for smoking cessation and one long-term study for evaluation of maintenance.

We have evaluated weight in these studies as main secondary endpoint. And the objective with rimonabant was to see to what extent the drug was able to reduce the usual weight increase that is observed in abstinent smokers. So, the objective was not at all to evaluate a weight decrease in this population but to prevent, try to reduce, the weight increase.

What we saw is actually the drug was effective to reduce the weight increase observed during the smoking cessation process.

DR. ROSEN: Michael, did you have another question? Unless there is any other questions,

this will be the last--oh, there is one more, I am sorry.

MS. COFFIN: Melanie Coffin, Patient Representative. I am curious. It goes to the population. Most of the group studied was caucasian women that were middle-aged. So, I am wondering should we be concerned for women in child-bearing years?

DR. ROSEN: Good question. Child-bearing age, the issue of approval.

DR. EGAN: I think that Dr. Davis-Bruno touched on this earlier about the teratogenic effects. Did you want to comment, Karen?

DR. DAVIS-BRUNO: I will comment briefly because I wasn't going to discuss the repro effects.

There are repro effects. There is also maternal toxicity concomitant with those reproductive effects seen in rats and rabbits, so that will be a review issue for the labeling.

DR. ROSEN: Good. Thank you.

DR. PROSCHAN: I just wanted to, you

know--because someone mentioned the sensitivity analysis without that smoking trial and it looks like certainly if you go by the risk difference, it looks like it is going to make a huge difference whether you include it or not because that confidence interval is very small for that smoking trial. And so I think it will have a huge difference there.

I don't know about when you look at the odds ratio, but at least for the risk difference.

DR. EGAN: I think Dr. Sahlroot would like to comment about that, please. He is our chief statistician.

DR. ROSEN: Great.

DR. SAHLROOT: Todd Sahlroot, Staff Team Leader.

Getting back to the--before I get to the risk difference, the odds ratio--that study did have a tremendous variance, the smoking study, not because there were 12 overall events but because one arm there were zero events, so that really does inflate the variance and the weight is inverse to

that.

So, there was a very small weight attached to a very large odds ratio. So, I don't have the exact data in hand, but I believe we did do that analysis and the odds ratio. When you remove that study from the total studies, the odds ratio came down. It was not as low as 1.3, which is what I think the sponsor had, but it was between 1.3 and our original odds ratio of 1.9.

The lower bound of the confidence interval, I think was below 1.

DR. PROSCHAN: Right. But the risk difference is what I am talking about. It looks like it would make a big difference whether you take it out or leave it in for that measure of the treatment effect.

DR. SAHLROOT: Yes, it would make a bigger difference there, because the confidence interval I believe was tighter, so, yes, that's true.

DR. ROSEN: Thank you.

Paul, you have one final question and then I think we are going to go to break before we deal

with the questions.

DR. WOOLF: A question for Dr. Mackie in slide 30. You had pair-fed mice, who were fed the same amount of food as the rimonabant mouse, but they lost more weight. Now, calories in equals calories out. Did they either burn more calories or did they waste more calories?

If they burned more calories, is this an increase in BMR, and would that translate that into potential weight loss in humans?

DR. MACKIE: This is the graph that was being spoken of. Basically, the observation is that the pair-fed animals lost less weight. The mechanism of this is not clear and I think is not too relevant for human use. It was just a motivator to look for an effect that may be peripherally mediated, which sort of led towards the adiponectin/adipocyte line of reasoning given that the adipocytes express CB1. But, if it's ground fat or something, it is not essentially meaningful for humans.

DR. ROSEN: Thank you very much.

I would like to bring this part of the session to a close. We have a 10-minute break and then the Committee will convene to discuss the questions and take a vote on each of the two questions.

The sponsor has asked me to recognize Judy Jones to come to the microphone, please, and declare your conflicts, as well as who you are, what you do, and give us a one-minute clarification of the European data sets.

DR. JONES: Thank you very much. My name is Dr. Judith Jones. I am President of the Degge Group, a drug safety consulting group.

A number of years ago I was head of the FDA's Drug Safety Group. I want to correct and put in context the data that was presented on the European data. It is very difficult to compare numbers of spontaneous reports but, in this particular case, it is critical.

The rimonabant program is the subject of stimulated reporting through both the postmarketing risk management plan you heard about earlier and

also a patient support program. Thus, the company is actually going out and getting reports so that, in part, explains the larger number of reports.

The second thing is that the reports come from the EUDRA [?] Vigilance program, and EMEA has not completed entering all the data for the older drugs.

Thirdly, the proportion of events that are seen are explainable by virtue of the fact that the two other drugs have other types of adverse effects, cardiovascular for sibutramine, and gastrointestinal for orlistat.

So, it is important to realize that you can't take those numbers literally.

[Break.]

Committee Discussion and Questions

DR. ROSEN: I will just remind the panel that we are not going to discuss diabetes as an indication for approval since that is a separate--and not piggybacked onto the weight-loss question for approval.

I am going to start with Dr. Jules Hirsch

to at least begin the discussion, and the first point that is raised is, please discuss your level of concern regarding rimonabant and psychiatric adverse events, in particular depression and suicidality, and neurological adverse events in particular, seizures, and the reasons behind your thinking on these issues.

I will then just entertain raised hands or we can go around the table and discuss the issues related to safety.

Dr. Hirsch, i would appreciate it if you would start, and please identify yourself one more time.

DR. HIRSCH: Yes. I am Jules Hirsch at Rockefeller University in New York. Your chairman is very kind letting me comment first. I unfortunately have to leave early, so I am glad to give you what comments I can.

I know it's our job here to tell what is good and what is bad about what the sponsor has presented us and what we are dealing with. There is much good about the rimonabant and all the

things you have heard today.

The greatest good I think is that people are trying to do something pharmacologically about obesity, which I needn't remind this audience about the extraordinary prevalence of it and its chief comorbidity, type 2 diabetes, and it is refreshing to hear about new things in this connection.

What also is good about it is the drug does lead to weight loss, there is no question about that. Now, I have a lot of other problems. However, having said that, the first problem I have with it is that, when I examined the weight loss curve, I note it seems familiar to me. It is exactly the same sort of weight loss curve that sibutramine gives and orlistat or Zenecal gives.

What happens is the weight comes down, the majority of it, about 5 percent more than placebo effect in the first 6 or 8 months, and then it sort of flattens out, but if you look carefully, just before a year or two, the inevitable is happening.

The weight is beginning to come back, and that happens with both of those drugs.

It seems to me--I didn't do the statistics on it--it looks as though we are headed in exactly the same direction with this drug. It is rather surprising to find the similarity of all of these curves because presumably the mechanism whereby this has occurred is a totally different thing with endocannabinoids, a very new and wonderful area. One would have anticipated something different. But perhaps what is happening in all of these cases, something else leads to the weight loss rather than a correction of a fundamental aberration that caused the obesity.

I feel strongly that we are learning more about these aberrations from the study of the drugs but that none of them is attacking fundamental causes including this one, in my opinion.

I have other problems with this also. I am delighted that some of the type 2 diabetes, the carbohydrate intolerance, and other problems are ameliorated during the weight loss, and I understand the statistical techniques of linear regression that help one evaluate just exactly what

percent of the variance in the carbohydrate intolerance is associated with, and related to, the weight loss, and what isn't, and that there is an independent effect.

I would doubt that very much, however. I think if one really wanted to know about that, the study that has to be done is that rimonabant has to be given to people specifically for that examination, and maybe that is being done or will be done, and great efforts made to maintain no weight loss, but exactly the same weight in a group of obese individuals, and study what happens with carbohydrate intolerance. Without such a study we may not really know that.

So, I am worried about any notion that this drug is better than others because of the good things that it does specifically with these comorbidities.

The problem with the whole thing, as I see it, is, number one, the number of people who are going to lose weight is fairly small. Apparently, about half of the people who are given the drug

will lose some weight, 5 percent or so of their body weight.

About a quarter of the group will lose the wanted 10 percent or so but, even in these circumstances, it is not much. Remember that we were presented several times with data that showed that when you tell people you are going to lose 17 percent of your body weight, which was picked because of what some drugs and stuff do for this, that people find that very disappointing. And this group will find it disappointing, too, those who are put on rimonabant.

You are telling a 220-pound woman that she has a sort of 1 in 4 chance of getting down to 200 pounds if she sticks with the program. Well, that is not going to make anyone very happy, but that is what we are getting out of it.

That is what people can expect and what is going to happen. Now, the question is, on the other side, what are the dangers with it. Well, I am not going to go into any great detail with this because you have heard it just as I have, and at

least I think everyone will agree there is a reasonable suspicion that we had better learn some more and watch this whole affair very carefully before we lunge into massive use of the drug for the benefits that I have mentioned.

Now, in order to take care of that, we were presented also with a wonderful new idea. It is called risk management action plan, and I think that is novel and is very interesting and exceedingly important. We are in desperate need of techniques for handling the Phase IV.

We know that only a fraction of adverse effects are usually reported now. We need new techniques for doing it. I worry, however, about the statement that the help of 20,000 physicians will be enlisted, each of whom will study I think 20 or 200, or whatever, patients and these data will be pooled and the patients will be managed in a special way.

If the sponsors really feel that can be done, I am sort of surprised, because it shows some lack of understanding of the sorry current state of

our health-care management in this country generally, that such a program could possibly be undertaken without the kinds of duress and so on that would probably be not suitable or legal or whatever in these circumstances.

In any event, the idea is a wonderful one, but I don't think we can do that, or I don't believe that can come about unless I misunderstood it completely.

Given this whole situation, therefore, I have come to the conclusion for myself that if I am asked to make a statement about this, I am glad the drug is available. I hope that lots more good work will be done, but I wouldn't in any way suggest that it be approved at the present time for use.

DR. ROSEN: Thank you, Dr. Hirsch.

So, in answer to the question, because I know you have to leave, 2a. Do you believe that the currently available data sufficiently characterizes its safety profile?

DR. HIRSCH: No.

DR. ROSEN: Thank you.

I think what we will do is we will go around the room and discuss Item No. 1 first and then come back for a vote on Item No. 2, and then go to the second question.

Paul, would you mind starting the discussion on Item No. 1 again, your level of concern about the safety issues, particularly the neurologic issues?

DR. WOOLF: Again, I am Paul Woolf. I think there is concern, and I am concerned about what we don't know and the dangers that we can fall into. We have a first in class. We have a whole bunch of studies that are in progress and particularly the stress, as I said before, that it did not appear that the sponsor had the requisite number of patients to meet the target of 1,500.

By the way, that number was reconfirmed less than four years ago at a committee meeting that I was participating in that agreed that 1,500 was the bar that needed to be reached for a one-year trial.

So, we don't have enough patients on here

for a long enough period of time to know what is going to happen down the road, and we have enough concerns. If the drug could cause a 30 percent weight loss, I think we would all be jumping up and down and throwing our hats in the air and say this is marvelous, and we might be willing to overlook the concerns.

But as Dr. Hirsch pointed out, this drug has about the same efficacy as the other two approved drugs. By the way, I think it's ironic that Aleve, the over-the-counter drug actually went to market today.

DR. ROSEN: I guess I could query you then as part of the voting, do you believe that the currently available data characterizes the drug's safety profile?

DR. WOOLF: That's up to the --

DR. ROSEN: I am sorry.

DR. WOOLF: Given what I said yesterday, I am not.

DR. ROSEN: You are not.

DR. WOOLF: I would vote no.

DR. ROSEN: You would vote no.

[Comment off mike.]

Okay. Go ahead, Eric.

DR. COLMAN: We received an e-mail last night from the company that was unopenable, and I was just approached by someone from the company who said--and I think I understand this; correct me if I am wrong--that the company sent us information to correct a table, and it now appears that the table that they sent us was not correct.

Is that correct? No?

DR. ROSEN: I think we are going to have to have you show us the table.

Paul, if you change your mind, we will go back and query you again this.

DR. GURAL: To answer your question, here is the exposure information from the long-term exposure in the Phase III for both one year and two years in the obesity trial plus the information on one year from the smoking trial. The combination of both the 5 and the 20 mg exceed the numbers of 2,000.

DR. ROSEN: Paul, do you want to talk about the guidance again, or Eric--

DR. WOOLF: I am just quoting. The indication was for the 20 mg dose, and I don't think you can adequately compare the 5--lump the 5 and the 20 mg together and say we have enough. We are going for 20 mg indication, do we have 1,500 patients who have been on the 20 mg dose? If it's 1,495 I could care less. If it's 1,100, that makes a difference

DR. ROSEN: Eric, can we get guidance on that? In the guidance it was 1,500 for the approved dose, is that correct?

DR. COLMAN: The original guidance was a little vague. It said 1,500 patients, but some people meant--does that mean 1,500 patients randomized or 1,500 complete? Does that mean every active dose or just the top dose?

I can tell you that internally, we never had any major issues with the number of patients that were studied in the rimonabant trials.

DR. ROSEN: So that settles that.

Paul, I will just query you again, you are not changing your mind?

DR. WOOLF: No.

DR. ROSEN: Okay. I would like to move to Dr. Gilman, please, if you can start the discussion.

DR. GILMAN: I will directly address the question. My level of concern regarding rimonabant and psychiatric adverse events is very high. In other words, I am very concerned that, first, there is a high dropout rate for various reasons. Second, there is a high proportion of people who develop suicidal ideation on high dose versus lower dose versus placebo. Therefore, I think this is a drug that needs further understanding with respect to what it does to people's psyche.

With regard to the neurologic problems, I am mostly concerned about epilepsy, less concerned about multiple sclerosis. It seems to me the data on multiple sclerosis are not definitive; that is, it could be that the events observed are within the natural course of frequency of multiple sclerosis

that we would expect without rimonabant. I don't see any direct tie to them except for that one case in which it appeared to exacerbate its symptoms. That is a possibility.

But with the seizure history, the seizure disorders, I went through these tables very carefully actually and I am struck that many of the patients who had a convulsive disorder did have a history of a previous epileptic episode of some sort even though the data we have are very sketchy.

There are probably three of those cases that did not have a history of previous epileptic seizure or frontal meningioma or an astrocytoma or some other cause for a seizure disorder.

So, it looks as if a previous history of a seizure does constitute a risk factor, at least in this group that were reported. All the same, seizures occurred more frequently in the rimonabant treated group 8 cases than in the placebo group 3 cases. So, I have concern about the neurology with respect to seizure disorders.

For the rest, I have already said it is

very unclear what these patients were experiencing, what do they mean by dizziness, what memory impairment do they have. I don't think we have adequate information despite the very large number of cases exposed. It's a huge number of cases with grossly inadequate data. What do they mean by memory disturbance? Is there anything objective about that?

What do they mean by lethargy? These are words, but they are not documented with anything that one can quantify. So, I am concerned about that.

DR. ROSEN: So, in querying you, do you believe that there is sufficient safety profile for rimonabant?

DR. GILMAN: I am concerned about the quality, not the amount of safety data.

DR. ROSEN: So, would you vote that there is or is not adequate safety data?

DR. GILMAN: Is not adequate, it's safety data.

DR. ROSEN: Thank you. Dr. Kreisberg.

Dr. KREISBERG: I am sorry that Dr. Hirsch said most of what I wanted to say, but I will paraphrase it to say that I am concerned about the relatively low frequency of adverse events that occur in the population that has been studied when you consider this might be extrapolated to a much larger group of patients who would be eligible for the drug.

Some rough calculations that I have made based upon only the psychiatric and neurological adverse effects, recognizing that some of them might be rather trivial, the absolute increase in risk is such that the number that you need to treat for harm is 6, and the number you need to treat for benefit of a 5 percent weight loss is about 4, and for a 10 percent weight loss is about 6. So it looks to me that the number needed to harm and the number needed to treat are pretty well balanced based upon the information.

DR. GOODMAN: Would you mind repeating that? This is Dr. Goodman speaking. Would you mind repeating that? I just wanted to hear that

again.

DR. KREISBERG: The percent of patients who have adverse neurologic and psychiatric events is about 12 percent higher in the rimonabant group than it is in the placebo group, and the number needed to treat, which is 100 divided by 12 is roughly about 8. So the number needed to treat for harm, the NNH, is about 8, 6 to 8.

If one looks at the absolute increase in weight loss as you use the rimonabant 20 mg dose, 5 percent versus 10 percent, the number needed to treat to achieve that particular benefit is somewhere in the neighborhood of 4 to 6.

So, overall, the relationship between the number needed to treat for harm and the number needed to treat for benefit is about the same.

DR. GOODMAN: I thought that was a very important point. I wondered whether the company--we could hear whether the company agrees with that and also whether or not it makes a difference whether you include or exclude the smoking-cessation study. I have some concerns

about us lumping the smoking-cessation study together with the obesity.

DR. ROSEN: I think this is such an important point I would like some clarification from the sponsor on that.

DR. GURAL: Could you please repeat the question, please?

DR. ROSEN: Basically, what we want to know is, if you calculated, as Dr. Kreisberg said, as the number needed to harm versus the number needed to treat for effective weight loss, it comes out about the same. The question, really, is have you done that and, if you haven't, why haven't you. And, if you have, what is your interpretation and does it include the smoking-cessation study which seems to be a bit different than the other ones in terms of the risk association.

DR. GURAL: Let me see if I can answer that question. We looked at the number needed to treat for 5 percent and 10 percent weight loss and, as Dr. Kreisberg said, it is about 5 to 6.

Now, as I showed this morning, for the

neurological events, the serious ones, the ones that require discontinuation, were very, very few.

Most of the neurologic events were transient. Most of the patients continued. They were not medically important, did not require hospitalization.

What we did do for number needed to harm was to look at depression. And, when you do the depression, it is about--I think it is 1 in 60 or 70. So, for depression, it is about 70. For the number needed to benefit--and this is only obesity--it is about 6.

You get comparable figures also for diabetes, in diabetes in terms of A1C reduction because A1C reduction is something that has been associated with clinical benefit. So we would say 5 to 6 and about 60 or 70 for the depression.

DR. ROSEN: Is that excluding the smoking cessation?

DR. GURAL: Yes; it is.

DR. ROSEN: Dr. Goodman, you can have the floor.

DR. GOODMAN: Yes; I just wanted to follow up on that. I am a little concerned about lumping all the psychiatric side effects in that number needed to harm. I don't think they are all equal in terms of severity of in terms of ramifications.

So I just--I like what you are trying to do in terms of comparing number needed to treat versus number needed to harm but I think we may be over-estimating the harms by lumping all the psychiatric and neurological together.

DR. GURAL: No; I was saying for depression only.

[Comment by sponsor off mike.]

DR. ROSEN: No, no, no. I think we are all set from the sponsor point of view. I think you made your point. Thank you very much. So let's have Dr. Kresiberg continue the discussion.

DR. KREISBERG: Well, I am not going to spend a lot of time rebutting that. You certainly are correct. We need to pick out the serious adverse effects. But the point of fact is, from other studies of intervention, it is frequently the

less serious effects that determine whether or not the patient will continue to take the medication or not.

Certainly, from statin studies, we know that the things that we can't quantify often determine the attitude of the patient about whether they will continue the medication.

The second thing is that I think the weight loss is modest and it has all of the characteristics that Dr. Hirsch described so elegantly. I, personally, believe that the sponsor's claim that the prespecified regression analysis accurately depicts what the weight-independent effects of the drug are on important metabolic parameters.

I actually like Dr. Arrone's more even-handed approach which is simply to say that the use of this drug was associated with reduction in cardiovascular risk without claiming that there was an additional mechanism beyond weight loss.

I, personally, believe that you would have to do the study to convince me that there was this

weight-independent effect. You might be interested to know that I looked up "deduced" because you use the term "deduced" in the briefing document.

In the dictionary, it says, "To reach a conclusion by reasoning, to infer from a general principle." That sort of implies that you don't need data to do it. I think you need hard data to make that claim and I don't think the data that you have is hard.

With regard to the question 2a, I am not exactly sure what that question means but I don't believe that there is sufficient safety data or sufficient data of safety of this drug to proceed.

DR. ROSEN: Thank you, Dr. Kreisberg.
Dominic?

DR. CIRUALO: Dom Ciraulo. I agree with what has been said. I just want to--I will summarize. From my perspective, I think that the reports of the psychiatric adverse effects are too high and too serious, especially given the attrition. I really think that--you know, you can argue when you lose so many people from a study

that efficacy is affected. You can argue it both ways. People leave because they are not getting better or because they have gotten better.

But I think what the real implication here is, you have lost data on adverse effects and I think you have lost serious data on depression and anxiety

The other issue I would like to emphasize is that anxiety is a serious psychiatric disorder.

It is not being afraid to talk to your boss. It is associated with suicide and it is not to be made light of. I think that we are somewhat underestimating that.

Then I think the other is the slide that was shown on aggression and the possibility that some of this anxiety may be more of a psychotic aggression nature. And I think that is a very, very serious problem.

I also think that the point that was made that subjects who have a baseline history of depression may be at higher risk but people who don't have a history of depression in the past are

also at risk. I am also not clear about treatment.

I really don't know what happens when these people get depressed or get anxious. I understand that some of them get treated, but I worry about follow up, how good the follow up is, and what the consequences are.

So, as far as--the only thing I want to say about neurological side effects, which is not my area, I think that some of them may seem minor.

Dizziness may seem minor. Balance may seem minor.

But somebody falls and breaks a hip. Somebody is in a car and has a seizure. That person is affected and society is affected.

So I would not minimize the neurological consequences that have been reported. So, essentially, I vote as the others.

DR. ROSEN: So I need to query you officially. Do you believe there is sufficient safety data for rimonabant?

DR. CIRAULO: No; I don't.

DR. ROSEN: Thank you very much.
Melanlie, could you introduce yourself?

MS. COFFIN: Hi. Melanie Coffin. I have to say that this is the first prescription drug advisory committee that I have sat on. The other one was for over-the-counter. So, obviously, with physicians stepping in, I assumed there would be a little bit more risk.

But I have to be very honest. As I was reading through the prep documents, my eyes got really big on quite a few issues. I think it is interesting that it has been a couple of times said that serious adverse events required hospitalization. But I would agree that a jump in anxiety is pretty serious to the individual that is actually having that.

I am concerned about the extrapolation of both the aggression in the males, or the suicides in the males, as Bob talked about and also the child-bearing. I think it is great, actually, that the sponsor did not intend to direct market for one year out of the shoot. But I will go back to what Lynn said and what I have experienced is that patients--people who are overweight and obese are

desperate, desperate, desperate, for any measure.

To see what goes on in the blogs on the websites, et cetera, word spreads like wildfire, whether there is good information to back it or not. Right now, doctors are not proactively addressing overweight and obesity with their patients and, often, it is the patient that is bringing it to them in the first place.

So I think, between those two things, you have got to watch it although I do appreciate the intent. I think that is fantastic. And I have to say, too, that the expectation of the patient--I would agree, that the patients, the dropouts, a lot of it has to do with the fact that they would like to have the weight off yesterday. And they would like all 50 pounds of it off, you know, before that.

So I think that safety data--it still makes me very uncomfortable. And so I would go with the rest of the panel on Question 2 that I would like to see a little bit more.

DR. ROSEN: So you would vote no?

MS. COFFIN: I would vote no.

DR. ROSEN: Thank you very much, Melanie.

Dr. Wang?

DR. WANG: I largely agree with what has been said so I won't cover that ground again.

DR. ROSEN: Phil, could you just identify yourself again?

DR. WANG: Yes; Phil Wang. I think, although we still have some questions about the data we have seen, it appears there is an important safety signal emerging with significant associations between the agent and depression and suicidality.

So I appreciate the sponsor's efforts to go sort of in a direction of finding a subgroup that they feel might be less at risk and still benefit. So your idea of identifying those who don't have a history of depression I think is the right direction to be going in.

Unfortunately, the data you showed indicate that the doubling of risk is still present in even the subgroup that doesn't have a history of

psychiatric illness.

So I think there is a need to then continue to pursue further other subgroup analyses that maybe might indicate a subpopulation in whom the cost/benefit, risk/benefit, analysis is favorable. In the data that were raised, the reason why I was asking those questions earlier, I think there is one potential candidate group and that is the folks with higher BMIs, the extreme obesity folks. It looks like there is some preferential efficacy in them. To my back-of-the-envelope calculation, it looks like you actually have lower risks of these adverse psychiatric events in that--maybe a group, you know, with, I don't know, BMIs greater than 40 or something.

But this is all going to take more data, I think, and more subgroup analyses to sort of explore this route. So I think I would vote that more data is necessary before proceeding.

DR. ROSEN: So you would vote no in terms of the currently available dataset?

DR. WANG: Yes. Yes; I agree with what you said.

DR. ROSEN: Thank you, Dr. Wang.

DR. GOODMAN: This is Wayne Goodman speaking. This is a real quandary for me. I recognize the need for additional medications. There are very few effective treatments for obesity out there. It seems to me one option might be to consider--is to identify more stringent prescribing guidelines in a group where--I just don't want to deny this option for a subgroup of patients out there.

I think that these psychiatric side effects are prevalent. Some of them are quite significant. Some of them represent hard endpoints whereas the others are softer endpoints. There is the risk that others have mentioned that there will be some proliferation, some generalization, to other populations where the risk may be higher.

One area where I would like to see--I wish we had some additional data--is the fate of those patients who wind up being terminated from the

trial or the treatment because of development of depression. I would like to know more about their long-term fate in terms of how long they need to be on anti-depressants or whether there is actually a possibility in the future of considering the combined use of rimonabant and an anti-depressant.

I understand why it was excluded from the trials.

It is hard for me, too, to try to think about my concern about a risk in the absence of the consideration of the benefit. I go back to the earlier questions I had about the quality-of-life data.

That, perhaps, troubles me more than anything else is that, when I try to reconcile--say, on one hand, well, it is clear that there is an efficacy signal. The patients are going to be enjoying some decrease in weight that has benefits, medical benefits, as well as some quality-of-life improvement.

On the other hand, it is offset by a diminished quality of life in other areas including the emotional and mental life functioning. I

understand that that may represent this disproportion of contribution of those patients who had the most adverse psychiatric events. Yet we are still left with looking at what the mean changes are. And they are pretty glaring in terms of the association between improvement and physical well being and emotional well being overall. So that probably gives me the most caution.

In terms of you want a vote? I guess I have said enough

DR. ROSEN: That's correct.

DR. GOODMAN: I would say that I would like to see additional safety data.

DR. ROSEN: So you would vote no.

DR. GOODMAN: I would vote no; yes.

DR. ROSEN: I just wanted to ask you a particular question. You seem to have focused on that quality-of-life issue that was presented in the slides by the sponsor. It seems to me that some of these were carryovers from their last visit before they dropped out. So we may be even underestimating the impairment in quality of life

because we are missing a whole group of people.

Michael?

DR. PROSCHAN: I am Michael Proschan. I think it is clear that there is a benefit of this drug. I am not sure that it is entire--well, I worry about the high dropout rate and I am not sure which way the bias goes when you use last observation carried forward. I mean, you would think, in certain ways, that that should make it look even worse for the drug because you would think that people who dropped out in the placebo arm may have been gaining weight and, if it continued, they would have gained even more weight.

On the other hand, they may have dropped out at a random high because, I am gaining weight, whereas, maybe if they had continued, they would have gotten over the hump, so to speak.

So it is hard to say which way that will go. But I think it is pretty clear that, even with that high dropout, there is some benefit of the drug on weight loss. Now, whether the effects on some of those other parameters is explained by

weight loss--I mean, I think there is certainly some evidence of that. I think they have presented some animal studies, the rat example where they tried to feed the rats the same amount as the ones that were on the drug and they still saw a difference, if I am interpreting that correctly.

And the statistical analysis that was done on these studies in people also suggests more than just the benefit you would see from the weight loss. But there is a problem with that analysis, I think, which is that, in regression analysis, you assume that the X variable is measured without error. In this case, it is measured with error and you are also interested in more sort of long-term weight loss.

And so those fluctuations in weight loss can actually cause it to look like the drug has some weight-independent effects when, in fact, there aren't any. I speak from experience on this because I am doing a very similar analysis in terms of trying to figure out how much of an effect was due to a blood-pressure reduction.

Anyway, the AEs, I have a high level of concern about all of them. I think, even if you look at the company's own tables, I think it is pretty clear that, for example, suicidal ideation is greater. I think neurological symptoms, depression, anxiety; these are biologically plausible.

I do appreciate the fact that ascertainment bias could be partially responsible.

I don't think it explains it all. And no long-term data. I worry about what is going to happen when a patient is on this drug for a longer amount of time. I also worry about the fact that heavier people, although they are apparently getting more benefit in terms of weight loss, the half-life of the drug is longer and so, presumably, they might get more of the adverse consequences.

I also worry about the fact that they may take more than they are supposed to. I mean, if I lose 10 pounds with this dose, I will double it. I will lose 20 pounds.

So, for all those reasons, I have a high

level of concern and I would also vote no.

DR. ROSEN: Great. Thank you very much.
Katherine?

DR. FLEGAL: Katherine Flegal. I think this drug could be of benefit to many people but I am also concerned, as everybody else is, about the--I think the data on safety are not definitive but are very worrisome and seem to have some degree of biological plausibility. There is the high dropout rate which may minimize the number of adverse events that were actually reported.

I think that this collection is sort of a post hoc collection of events and symptoms that really have not been adequately investigated enough in detail because they weren't identified in advance.

That being said, I think we need to err on the side of caution in this case because I think one reality is that a lot of overweight and obese people are desperate, first of all not necessarily for health reasons but for cosmetic reasons and that we know particularly a lot of women are very

desperate about weight, not necessarily for health reasons.

Other research suggests that the proportion of people--there's a quarter to a third of people who are using prescription weight-loss medications are not actually overweight or obese and are not very responsive to safety considerations. So I think there is a large pool of people who may not really realize the benefits of the drug but could only realize possible adverse events and that would include a lot of people who have BMIs below 27, many of whom are probably going to be women because, down to a BMI of about 21, about half of women consider themselves overweight and would like to weigh less. These are extremely high numbers that people may not realize how high they are.

Also, lean people who smoke, a frequent reason for this failure of smoking cessation is weight gain. So you have lean people who are smoking in part to reduce their weight who may be inclined to try to use this drug to keep their

weight low. Again, they would already be people at low weight.

Obviously, people with diabetes could benefit from weight loss. But it seemed from the data presented they may experience somewhat less weight loss and also somewhat more potential harm in this case. So they may also not benefit.

So, all those things taken into account, I would say I would also vote no, we don't know enough.

DR. ROSEN: Good. Thank you, Katherine. Jessica?

DR. HENDERSON: Hi. Jessica Henderson. I have very high concern about the safety data. When you look at the lifetime exposure in the animal studies, it is very clear that we need more long-term data in humans and especially, like has already been said, we are going to have massive use of this drug and we just have a very small group of people for a two-year study. But yet this is presented as a drug that is going to be lifetime because it is a chronic--obesity is a chronic

disease; therefore this will be long-term use.

But we don't have long-term data. I don't consider two years long-term data. I would at least want to come back to this after the CRESCENDO study comes back and at least have some five-year data.

The target population in these studies were more middle-aged and older women and that just reminds me of hormone therapy, being told that women should be on hormone therapy forever, breast-cancer survivors being told they should be on tamoxifen forever. And then we got the long-term data and it was wrong and literally millions of women were put at risk.

So that is my primary concern is the long-term data. And I agree with everything else that has been said. So I vote no.

DR. ROSEN: Thank you.

Tom?

DR. CARPENTER: Tom Carpenter. My comments are somewhat influenced by the very impressive scientific background to the system that

this drug manipulates and the highly conserved nature of the receptor through biology and the evidence that this is a very basic biological--is regulating a very basic biologic function in the CNS.

It is not a system that is directed specifically to appetite alone. Hence, I think the side-effect profile that we see reflects that. I think that there is very significant concern about particularly the depression and suicidality issues.

I am a little bit less concerned but may have to do with the limited numbers in terms of--and definitions--related to the seizure data.

But I think, also, when one looks overall at the CNS data together in whichever analysis you see, there is considerable concern.

Moreover, we may be underestimating that, in part, because of the high attrition rate of the study. We tend to look at these numbers thinking in terms of percent of patients enrolled. If you convert how you are thinking about that to the actual patient exposure and you think of it in

terms of patient years, many of the patients that had adverse events and left the study because of that were exposed for brief periods of time and those numbers, then, change, I think, to a more significantly worrisome ratio.

Finally, I think there was one comment about the way future studies might be more directly presented to the committee in, say, the CRESCENDO study and others to yet be analyzed. If possible, it may be nice to have proactive plans and potentially even agreement between the company and the agency to agree upon a similar method of analysis so that some of the methodological issues that came up in the way the data was presented today could be avoided.

So, briefly, a no vote for 2a.

DR. ROSEN: Good. Thanks, Tom.

Ken?

DR. BURMAN: I am going to be succinct. I agree with most of the comments that were mentioned earlier. I do want to emphasize the dilemma of trying to balance the pros and cons of this

medication and also emphasize the divergent conclusions that are apparent to me from the sponsor and from the FDA.

I am concerned specifically about the longer-term effect over several years of this agent not only with the neurologic symptoms just noted but also with other things such as reproduction and hypertension.

I am concerned that the studies were done in mainly caucasians and may or may not apply, as was implied, to other ethnic groups. I am concerned about the ability of previous psychiatric disease as a screening method to predict whether somebody who is put on rimonabant will develop further psychiatric disease, and there obviously was a discrepancy between the two presentations.

I would like more specific information, which didn't seem to be given, on the European study, that they are ahead of us by a year and have specific information on, again, some flaws but, nonetheless, theoretical flaws, postmarketing studies. But I don't have a good feeling exactly

what are thought to be rates of the psychiatric neurological symptoms in the postmarketing studies from Europe.

All that having been said, I must come to the conclusion with the rest of the panel that the answer is no.

DR. ROSEN: For 2a.

DR. BURMAN: For 2a.

DR. ROSEN: Steve, you are a non-voting member but we would like to hear your opinion.

DR. RYDER: I just have one comment. Thank you, Dr. Rosen. My comments are not specifically directed to the NDA but just some thoughts and observations on just the general discussion that I have had the privilege of hearing today.

It is helpful to have as much specificity in the guidance as possible, and some of these comments may have some relevance there, and try to minimize any differences. Paul Woolf, I, and some of the others here on this committee sat through a couple of discussions that have taken place and

just the idea of how many patients, for example, at one year, at two year, on top dose--Eric, some of the things that you mentioned, and I know that the CDER staff have been very generous with their time in trying to help sponsors and other investigators.

I just want to encourage that so that development can be as efficient as possible and, hopefully, it can proceed to a positive outcome. But that is very helpful.

DR. ROSEN: Thanks, Steve.

So I am Chairman and I can talk as long as I want. But I am going to be very brief. I just want to emphasize two points. One is what is amazing is the biology of this system in that we don't really fully understand it. But, as Dr. Hirsch and others have pointed out, this drug works.

But it works through a different mechanism. I think that is actually exciting, that you can get weight loss through this system. But what I am really troubled by is the lack of good safety data. So if you were going to design a

study in which you knew you were going to block these receptors, it would be very clear, I would think, that you would want to look very carefully at these adverse events.

Now, in clinical research, and I have done it for a living for 20 years, AEs are not a big deal usually. They are recorded by the monitor or the nurse or whoever is in the clinic or the physician, and then they are checked off. But, in this particular case, the adverse events, not the serious adverse events, but the adverse events tell the story.

And we don't have enough information. I think that, in retrospect, when we look at the system that we are acting on with this agent, we need that information. I think Dr. Gilman appropriately asked very specific questions about these adverse events.

So they are a big deal and they are serious and, until we really know that information and we know the true prevalence of these adverse events, I think we can't make a decision.

So I think the sponsor has done a very reasonable job. They have worked with C-CASA. They have worked with the FDA. They have tried really hard. I think I would go back and ask the question, why weren't these more detailed at the beginning of these big trials when we knew that this is a central-nervous-system-acting agent that is going to have these kind of effects.

Until we have that information, I think it is very difficult for us as committee people to make those kind of judgements. So I would vote no and I already see a comment from Michael.

DR. PROSCHAN: I was going to say, in future trials, I think Dr. Posner's suggestion about measuring these things in a systematic way to eliminate this possible bias, ascertainment bias, it really important.

DR. ROSEN: Okay. I would like to move to Question 2 and I think that we have already talked somewhat about additional data. But I would like to open up the floor before the vote about what people would like the sponsor to do.

I think one thing that we have heard is the CRESCENDO study is going to be a very important study. But, again, it has to be so that the adverse events are coded and are properly interpreted and reviewed in an independent way so that we can get a good analysis.

I know the sponsors are working with C-CASA on this in a prospective manner. I would like other comments if people have any comments about what else the sponsor can do to obtain additional data.

Wayne, do you have comments?

DR. GOODMAN: Yes. I guess one of the deciding factors for me and, obviously, you could tell I was on the fence on this, was thinking about the chronicity of administration and the time course of both the changes in weight--and there is some suggestion that there is a plateauing, at least, in changes in weight.

I would like to know more about the time course, then, of the psychiatric symptoms. I think that has been described, but in a more anecdotal

way. If there was additional information that the company could provide now, I would still be interested in hearing that if that was okay with the Chair.

But my concern is that two years out, or three years out, when these patients are still taking it, that the risk/benefit ratio between the psychiatric or neurological symptoms and the benefit is going to change to a less favorable balance.

DR. ROSEN: I will take Dr. Gilman first and then Paul. I wanted to ask you, Dr. Gilman, as well, to comment on what you would want the sponsor to do as we move along in this process.

DR. GILMAN: Sid Gilman. As I indicated earlier, I would like to have more specific information about what the subject, the patient, means when he or she says "dizzy." There should be a subgroup kind of list that one can tick off and get more specific information and find out if they are all experiencing something similar or there are disparate symptoms. I think any neurologist could

help you determine what kind of list you would have.

For a second, I would like to see some better characterization of the seizures prospectively so that we get the best data we can.

Now, I say that and I say prospectively. I understand that you can only get retrospective data from seizures. But it has to be obtained from the observer who was there with the patient or the patient, himself, herself, to find out exactly what happened. Was there an aura? Was there a falling-down episode? Was there shaking? Was it unilateral? And so on.

So I just think the quality of the data needs to be improved for these side effects.

DR. ROSEN: So that raises an interesting question that I just would like to ask Eric about and that is, you know, we have our classic definitions of serious adverse events. When we go through serious adverse events, it is quite detailed and the information is quite specific.

Is there any role for thinking about

seizure as a serious adverse event or, in some way, upping the documentation so that this process will be much more inclusive? I mean, seizure in an individual who has not had a seizure is a big deal.

DR. COLMAN: I think what we would do in that case is consult with our colleagues internally in neurology and see what they--of course, they deal with trials of people who have seizures. But they still might be a place to start.

MR. FRANCO: Thank you. Paul?

DR. GOODMAN: Let's face it. There is never enough safety data. You can always want more. No one will argue that more is better but then there is reality. But, in fact, we have reality; that is, we have a drug that is approved in the U.K. and in Germany and in 35 other countries.

I wonder if it is possible to piggyback on that experience something more than just a conventional postmarketing survey which we have heard about ad nauseum at these meetings which really turns out to be not much, and that is to do

a very detailed, very prospective, study of a subset of these patients from now until whenever and use that information to come back and make us all feel nice and happy without having to spend a whole lot of money going out and developing a new trial from scratch.

DR. ROSEN: So you are suggesting Phase IV for European studies.

DR. WOOLF: Well, no; not as classically defined. How about if 3c?

DR. ROSEN: Other comments?

Yes, Dominic?

DR. CIRAULO: Dom Ciraulo. I think we have to take a different approach to the adverse effects that we have seen here. I don't think we can treat it like we do in the usual clinical trial. I don't even think something like the safety GI is something that would work in this.

I think you highlighted the area--I will just stick to my area, depression and anxiety. I think you have to treat it almost like an outcome study, that you want to get together, get a group

together, get the best scales to measure anxiety, depression and other psychiatric symptoms along with the Columbia Group's suicidality methodology.

I think that is really sort of a shift from the way we think about measuring AEs because AEs seem to have become the focus of what we are talking about.

DR. ROSEN: Thank you.

Melanie?

MS. COFFIN: I would love to know more about the dropouts but you can't really do a whole lot about that. What I would like to see that might be possible is more information on the patients that are discontinued because they are put on anti-depressants, just a little bit more follow up on how long, what severity, et cetera.

DR. ROSEN: Michael.

DR. PROSCHAN: Also related to this discontinuation because of going on anti-depressants, to me that should not cause discontinuation of the study. I mean, if your drug causes people to get depressed and, therefore, they

have to go on anti-depressant and stop taking the drug and they gain a lot of weight, that is one of the consequences of the drug.

If it causes more depression, then that is a consequence of the drug. So, to me, that is not--I don't find that to be an acceptable thing to drop people when they have to go on anti-depressants.

DR. ROSEN: Right. So I think your point is very well taken. I think we have to distinguish the terms. If it is discontinuation but follow up at the end of the study, that is one thing. But dropout, or not follow a patient because they have now gone on the anti-depressant is another thing.

And I think it is really essential that that data be obtained. I absolutely agree. Tom?

DR. CARPENTER: How difficult would it be to go recover the patients that have been discontinued? There may be a wealth of data in this 50 percent that is not there. I think that would be a goldmine of completing this dataset.

DR. ROSEN: Dr. Gilman?

DR. GILMAN: I would be very cautious here. I think one would want to assess in the patients who became depressed if they stay in the trial and remain on rimonabant, you would want to be darned sure that they are being monitored carefully despite being put on anti-depressants because anti-depressants may be very weak in comparison to the depression that results from this drug.

So I would be very cautious.

DR. ROSEN: I think what Michael was referring to was just continuing to follow these patients on anti-depressants but not on active drug. In other words, just continue them in the study without active drug. Bob?

DR. KREISBERG: Well, you know, I think the sponsor has taken a big hit here and I would like to say that I think they have done a terrific job in trying to bring a unique drug to market and that--if some of you remember Woody Hayes. Woody Hayes was an Ohio State football coach and he said he needed help on Saturday afternoon, not on Monday

morning and we are giving you Monday morning advice.

It is easy to target the defects but what we really need to do is we need to work closer, I think, with you to design studies that would be satisfying and address some of these issues. And I really do think that my colleague's insightful comments about this particular system should allow us to identify areas for sort of targeted evaluation right from the very beginning.

I, personally, don't think there is much you can do with the trials that are already underway. They are what they are and they probably all suffer from this lack of specificity about definitions. So I think it is going to be hard to mine that information.

But I do think that this is a unique drug and it works through a unique system. Even though it is not as wonderful as everybody would like it to be, I can tell you, looking at the evolution of oral hypoglycemic agents and the treatment of diabetes over 40 years is that each iteration, each

generation, gets better and better. I think you have to start at this particular point and continue to evolve.

The things that I think are really important, in addition to better characterization of the adverse effects through redesigning how you are going to evaluate them is I think the diversity issue raised by Ken is absolutely crucial because not only does it minimize the utility of the drugs in African-Americans, there is no data on Hispanics who really suffer from this problem.

So I think that that becomes a crucial issue for generalization of your recommendations and claims. I do believe that head-to-head studies, looking at the metabolic changes that occur when you compare your drug with either other drugs or other forms of weight loss where you can actually get comparable degrees of weight loss, and then claim that there is something magical about this drug that goes beyond weight loss.

But I think that most of us in the field are not going to buy that right now based upon the

data. And I think that is an important issue that you have and it would be an important marketing tool if you could actually prove that.

DR. ROSEN: Thank you, Bob. Do I hear any other comments? We are going to go to a vote but, before we do, I have to admit that I forgot to announce the vote for Item 2a. The vote for 2a, to those of you in the remote situation, is 14 no and none yes.

Having gotten that out of the way, I will then ask for a vote, individual vote, on Item 3a. The question is, and I will start with Paul, based on the current data--I won't repeat the question for everybody--based on the current data, do you believe rimonabant has a favorable risk/benefit profile and should be approved for the indication of weight management in individuals with a BMI greater than 30 and 27 when accompanied by at least one comorbid condition.

DR. WOOLF: No.

DR. ROSEN: Dr. Gilman?

DR. GILMAN: No.

DR. ROSEN: Dr. Rosen says no. Dr.
Kreisberg?

DR. KREISBERG: No.

DR. ROSEN: No.

DR. CIRAULO: No.

MS. COFFIN: No.

DR. ROSEN: Dr. Wang?

DR. WANG: No.

DR. ROSEN: Dr. Goodman.

DR. GOODMAN: No.

DR. ROSEN: Dr. Proschan?

DR. PROSCHAN: No.

DR. ROSEN: Dr. Flegler?

DR. FLEGLER: No.

DR. ROSEN: Dr. Henderson?

DR. HENDERSON: No.

DR. ROSEN: Dr. Carpenter?

DR. CARPENTER: No.

DR. ROSEN: Dr. Burman.

DR. BURMAN: No.

DR. ROSEN: Okay. So the vote--I'm sorry;
I have one point of clarification. Dr. Hirsch also

voted no and he voted no on 2a. So there are 14 votes no, no votes yes, on Item 3a.

I think we have discussed 3b. I think there is a lot more discussion to be had. I am just looking around the committee to ask if anybody on the committee would like to add some additional comments about what additional information they need.

I would like to echo Dr. Kreisberg's comments. This is a new class of drugs and the sponsor has gone out of its way to do as much as they possibly can with the information they have. I think we all look forward to more data.

I think this is an exciting area. I think there are tremendous opportunities and I think we are looking forward to working with them, both at the FDA level and at the committee level in the future.

If there are no further comments, I would like to officially adjourn this meeting.

[Whereupon, at 4:19 p.m., the meeting was adjourned.]

386

- - -

<p>"</p> <p>"modulation ^[1] 226:2</p> <p>"there ^[1] 226:1</p> <hr/> <p>\$</p> <p>\$1 ^[1] 71:15</p> <p>\$175 ^[1] 240:10</p> <p>\$275 ^[1] 240:10</p> <hr/> <p>)</p> <p>rgan ^[1] 276:8</p> <hr/> <p>0</p> <p>0.001 ^[1] 227:10</p> <p>0.0283 ^[1] 317:4</p> <p>0.06 ^[1] 131:19</p> <p>0.1 ^[3] 124:21 133:19 145:12</p> <p>0.1077 ^[1] 317:7</p> <p>0.11 ^[1] 120:12</p> <p>0.14 ^[1] 119:22</p> <p>0.15 ^[1] 133:18</p> <p>0.16 ^[1] 131:20</p> <p>0.17 ^[2] 132:4,6</p> <p>0.2 ^[1] 131:19</p> <p>0.23 ^[1] 131:19</p> <p>0.28 ^[1] 120:12</p> <p>0.3 ^[1] 293:2</p> <p>0.30 ^[1] 119:22</p> <p>0.36 ^[2] 112:21 121:17</p> <p>0.4 ^[2] 145:9 162:19</p> <p>0.40 ^[1] 116:1</p> <p>0.44 ^[1] 272:4</p> <p>0.5 ^[5] 88:3 163:9 263:10 270:2 313:18</p> <p>0.6 ^[1] 126:2</p> <p>0.62 ^[1] 112:21</p> <p>0.65 ^[1] 121:17</p> <p>0.68 ^[1] 131:22</p> <p>0.7 ^[1] 87:1</p> <p>0.8 ^[1] 277:21</p> <p>0.89 ^[1] 317:6</p> <p>0.9 ^[1] 124:21</p> <p>0.94 ^[1] 272:6</p> <p>06 ^[4] 144:9,10,18 145:8</p> <p>07 ^[1] 311:15</p> <hr/> <p>1</p> <p>1 ^[55] 4:3 23:4 39:3,22 87:15 91:17 94:18 97:17,17 98:17 104:21 106:8 109:22 111:5 112:17,18 113:19 114:7,18 116:16 117:10 119:21 124:19 131:22 132:7,20 133:6,8 148:8 176:19 185:8 194:19 210:1 217:1 232:8 247:22 263:14 271:2 272:10,10 275:7 277:22 283:7 285:3,4,8 291:15 310:8 313:22 316:18 325:11 333:14 336:2,6 346:9 1,000 ^[5] 40:5,6 42:15 272:4,5 1,100 ^[2] 309:21 339:9 1,134 ^[1] 311:6 1,235 ^[1] 318:16 1,300 ^[1] 78:2 1,495 ^[1] 339:9 1,500 ^[8] 309:5 336:16,19 339:7,12,15,16,17 1-year ^[2] 76:4 86:1</p>	<p>1.0 ^[1] 317:3</p> <p>1.08 ^[1] 133:6</p> <p>1.1 ^[3] 114:9,14 275:20</p> <p>1.2 ^[1] 263:12</p> <p>1.3 ^[6] 108:11 114:7,11 116:13 325:7,8</p> <p>1.4 ^[5] 114:14 144:19 145:9 261:20 290:4</p> <p>1.5 ^[2] 75:2 270:3</p> <p>1.6 ^[2] 114:13 317:5</p> <p>1.69 ^[1] 132:18</p> <p>1.7 ^[7] 108:9 263:9 264:18 278:16,18 279:1 317:2</p> <p>1.8 ^[3] 114:13 278:19 286:7</p> <p>1.8-fold ^[1] 227:12</p> <p>1.9 ^[5] 114:9,11 278:7 285:22 325:9</p> <p>1.93 ^[2] 286:11 316:22</p> <p>1/2 ^[2] 128:17 314:22</p> <p>1.00 ^[3] 8:11 221:5,8</p> <p>10 ^[25] 3:8 16:19 53:15 63:15 71:17 72:6,10 74:8 75:10,14 82:1,8 114:22 117:19 118:12 155:12 210:7 212:1 244:20 283:21 333:4 343:16 344:11 345:20 361:20</p> <p>10-minute ^[1] 327:2</p> <p>10-week ^[1] 115:2</p> <p>10-year-old ^[1] 17:17</p> <p>10.5 ^[2] 33:9 80:4</p> <p>100 ^[6] 78:16 113:7 176:14 210:8 293:1 344:6</p> <p>100,000 ^[5] 117:5 135:1 165:20 293:12 314:17</p> <p>1008 ^[1] 94:11</p> <p>104 ^[1] 259:11</p> <p>106 ^[1] 104:22</p> <p>11 ^[8] 18:4 97:14 102:6 111:6 162:4 163:12 228:11 277:18</p> <p>11,225 ^[1] 275:5</p> <p>11:15 ^[1] 185:3</p> <p>11:20 ^[1] 185:4</p> <p>11:55 ^[1] 221:7</p> <p>110,000 ^[1] 40:17</p> <p>113 ^[1] 275:6</p> <p>117 ^[1] 295:15</p> <p>1190 ^[1] 94:10</p> <p>12 ^[16] 66:3,4,10 80:20 83:9,18 125:14 148:8 154:4 185:7 260:21 309:6,21 324:20 344:4,6</p> <p>120 ^[1] 209:5</p> <p>1201 ^[1] 283:11</p> <p>129 ^[1] 62:14</p> <p>13 ^[6] 1:7 117:7 284:6 285:9 290:3 292:4</p> <p>13,000 ^[1] 94:16</p> <p>13.5 ^[1] 81:9</p> <p>13.6 ^[1] 98:20</p> <p>130 ^[1] 182:5</p> <p>137 ^[1] 272:7</p> <p>139 ^[1] 266:8</p> <p>14 ^[9] 64:1 117:5,8 259:8 277:6 283:20 296:15 383:8 385:1</p> <p>14,000 ^[3] 40:18 41:20 100:17</p> <p>14,280 ^[1] 97:15</p> <p>14.1 ^[1] 262:10</p>	<p>140 ^[1] 3:22</p> <p>140,000 ^[1] 40:22</p> <p>15 ^[7] 3:10 83:10 88:7 104:3 123:10 163:8 296:17</p> <p>15,000 ^[3] 40:4,19 94:9</p> <p>150 ^[1] 174:17</p> <p>153 ^[1] 318:16</p> <p>158 ^[1] 3:24</p> <p>16 ^[11] 42:21 75:11 83:18 84:12 209:8,10 258:1 271:4,16,22 272:18</p> <p>16.7 ^[1] 290:4</p> <p>1600 ^[1] 256:21</p> <p>17 ^[3] 71:11 162:16 333:7</p> <p>17,000 ^[2] 41:11 299:7</p> <p>17.6 ^[2] 279:22 318:11</p> <p>170 ^[1] 3:25</p> <p>18 ^[3] 40:15 43:12 163:10</p> <p>183 ^[1] 311:9</p> <p>185 ^[1] 3:28</p> <p>19 ^[4] 80:12,14 131:17 271:3</p> <p>1964 ^[1] 50:11</p> <p>1980s ^[1] 183:8</p> <p>1990 ^[1] 294:18</p> <p>1994 ^[1] 51:17</p> <p>1996 ^[2] 38:3 252:4</p> <p>1998 ^[3] 38:17 294:18 296:14</p> <p>1999 ^[1] 296:17</p> <p>1A ^[1] 143:3</p> <p>1st ^[2] 97:14 293:11</p> <hr/> <p>2</p> <p>2 ^[84] 4:6 37:5 39:15 40:1 41:14 43:19 44:10 50:3,7 62:1,3,5 64:16 65:15 68:7,17 69:13 70:3,5 72:17 74:3 76:12 77:4,7 81:1 83:20 84:11,22 85:15 86:2 87:14 88:18 91:20 92:7,9,21 93:18 94:18 95:21 96:12 98:15,22 103:15 106:8,9 109:22 113:19 120:7,9,12,16,16 125:8 126:12 130:22 132:15 138:22 168:15 169:9,17 210:1 216:21 217:1 226:16 232:8 244:9,13 245:9 253:6,10 265:9 270:2 271:1,17 272:12 277:22 283:7 309:6 314:22 330:6 331:18 336:3 353:20 372:19</p> <p>2,000 ^[3] 116:6 209:1 338:22</p> <p>2,400 ^[1] 156:5</p> <p>2,734 ^[1] 295:6</p> <p>2-arachidonoylglycerol ^[5] 50:18 61:17 62:4 188:1 193:4</p> <p>2-fold ^[4] 107:1 112:22 198:21 220:19</p> <p>2-year ^[1] 76:2</p> <p>2.1 ^[4] 99:6 122:21 125:8 278:22</p> <p>2.2 ^[2] 108:9 126:1</p> <p>2.3 ^[1] 114:8</p> <p>2.5 ^[3] 120:12 227:8 248:2</p> <p>2.7 ^[2] 272:3 313:18</p> <p>2.7-fold ^[1] 43:3</p> <p>2.8 ^[1] 317:3</p> <p>2.9 ^[1] 281:11</p> <p>20 ^[115] 23:15 32:5 39:21 42:8</p>	<p>63:17 70:4 74:21 75:10,16,20 76:17 79:11,16 80:4,13 81:14 82:4,12 83:8,15 84:21 86:5 91:9 92:3,8 94:17,18 96:6,7,11,12,14 97:17 109:10 111:18 113:20 114:22 115:12,21,22 116:3,4 122:4 123:11 124:10 126:13,17 131:1,1,19 132:6,18 133:4,14 158:3 175:13 176:16 177:11,15 179:8,17,22 184:10 205:18 208:8 211:2,17 213:6,13 226:20 228:15 247:17,20,22 248:15 252:21 256:18 257:18 259:9,13 267:22 269:22 270:2 271:1,17 272:4,11 275:17,20 277:1 281:6,20 283:22 284:22 285:5,21 286:22 287:2,10,12 292:22 309:10,22 311:3,6,20 334:17 338:21 339:4,6,7,8 344:10 361:21 371:6</p> <p>20,000 ^[3] 155:10,11 334:15</p> <p>200 ^[3] 57:4 333:14 334:17</p> <p>200-patient ^[1] 311:11</p> <p>2000 ^[1] 38:17</p> <p>2003 ^[1] 14:4</p> <p>2004 ^[2] 14:6 229:7</p> <p>2005 ^[2] 43:14 45:4</p> <p>2006 ^[8] 43:15 44:5 45:7,13 215:2 229:7 258:22 311:15</p> <p>2007 ^[7] 1:7 38:3 117:9 119:16 252:16 259:2 293:11</p> <p>2010 ^[1] 299:13</p> <p>208 ^[3] 77:21 295:14,15</p> <p>20s ^[1] 133:17</p> <p>21 ^[6] 111:6 134:5 228:10 238:22 295:19 363:13</p> <p>21-888 ^[1] 1:4</p> <p>215 ^[1] 3:29</p> <p>2176 ^[1] 311:21</p> <p>218 ^[1] 71:10</p> <p>22 ^[1] 109:5</p> <p>220-pound ^[1] 333:13</p> <p>223 ^[1] 4:3</p> <p>22nd ^[1] 118:8</p> <p>23 ^[3] 83:6 163:7 254:2</p> <p>230 ^[1] 77:21</p> <p>235 ^[1] 4:6</p> <p>24 ^[2] 261:13 309:7</p> <p>243 ^[1] 4:10</p> <p>2474 ^[1] 95:20</p> <p>25 ^[3] 34:18 43:22 80:17</p> <p>250 ^[1] 311:21</p> <p>251 ^[1] 4:15</p> <p>26 ^[1] 277:5</p> <p>27 ^[10] 13:6 38:15 47:4 73:8 74:11 241:10 242:6 296:20 363:12 383:18</p> <p>27.4 ^[1] 261:12</p> <p>29 ^[4] 33:7 119:16 126:15,21</p> <p>2a ^[8] 335:18 349:10 367:16 369:7,8 383:7,7 385:1</p> <hr/> <p>3</p> <p>3 ^[28] 4:10 62:14 75:10 100:13,14 109:22 113:18 114:9 118:3 124:11 128:5,17 132:5 148:</p>
---	--	---	--

<p>8 154:3 206:1 228:7,12 275:1 1 277:21 280:18 283:7 285:1, 6,7 286:14 306:11 341:19 3,000 [2] 183:14 259:10 3,478 [1] 94:18 3-day [1] 123:19 3-month [1] 46:4 3.03 [1] 317:6 3.1 [3] 263:11 265:12 278:15 3.2 [1] 99:3 3.3 [1] 264:4 3.5 [2] 124:12 261:18 3.68 [1] 228:13 3.8 [1] 122:22 3.9 [1] 108:9 30 [18] 13:5 34:18 38:15 47:6 69:20 73:10 74:12 79:2 117: 6 119:8 162:11 210:8 229:7 293:10 300:9 326:3 337:3 383:18 30,000 [1] 33:10 300 [1] 293:4 300-patient [1] 311:10 301 [1] 386:3 31 [1] 130:14 32 [3] 229:19 254:1 318:9 32.2 [1] 279:22 3200 [1] 131:17 328 [1] 4:16 33-year-old [1] 287:10 34 [1] 171:1 34A [1] 43:2 35 [6] 70:6 73:12 119:18 162: 17 242:9 376:16 36 [2] 3:13 163:6 36-year-old [2] 117:17 286: 22 3600 [1] 131:17 37 [3] 40:14 43:11 293:11 38 [2] 71:10,12 384 [1] 295:4 39 [1] 285:1 3a [2] 383:11 385:2 3b [1] 385:3 3c [1] 377:10</p> <hr/> <p style="text-align: center;">4</p> <hr/> <p>4 [31] 23:5 63:16 64:15 72:19 76:1,14,15,22 79:20 80:15 81:12 83:20 96:18 100:14 103:11 104:21 109:22 111:5 119:21 160:21 176:22 206:4 259:11 261:13 271:1 277:20 283:7,18 333:14 343:15 344: 13 4,000 [3] 109:1 182:1,1 4.1 [2] 125:7 281:8 4.5 [1] 103:10 4.7 [2] 98:20 176:15 4.8 [1] 281:10 4:19 [1] 385:21 40 [12] 66:10 78:3 104:14 118: 11 123:14 174:12 176:21,21 283:21 308:7 355:15 381:22 400 [1] 174:17 41 [2] 177:22 318:21 42 [3] 70:8 170:19 171:14 43 [1] 104:21</p>	<p>441 [3] 256:22 257:5 311:7 45 [2] 25:16 229:19 46 [1] 284:21 47 [1] 171:1 4796 [4] 284:7,13 285:13 315: 8 48 [1] 111:6 488 [1] 95:21 49 [3] 3:15 254:1 315:9 49-year-old [1] 128:13 495-5831 [1] 386:3</p> <hr/> <p style="text-align: center;">5</p> <hr/> <p>5 [78] 3:3 72:6,10 74:8 75:10, 14,15,19 76:17 78:2 80:15 81:22 82:5 86:21 92:18 96:8 110:2 111:13,17,20 112:2,4,7, 8 114:21 115:8,11,13,15 116: 6 118:22 119:1 121:20 126: 13,17,18 127:20 128:21 174: 18 177:2,7,12,14 206:21 217: 7 244:20 252:12,13 253:1 257:18 267:18 271:2,17,17 277:18,19 279:4,7 283:8,21 284:13 285:3,14 286:6,21 290:10 316:3,12 330:17 333: 1 338:21 339:5,5 343:15 344: 10 345:20,21 346:17 5,000 [1] 111:16 5,400 [1] 40:7 5.4 [1] 264:4 5.6 [1] 262:15 5.9 [2] 99:6 122:19 50 [7] 25:14 113:13 123:14 174:13 299:10 353:16 379: 20 500 [1] 309:6 54 [1] 295:18 567 [1] 295:5 58 [2] 72:21 254:2 59-year-old [1] 266:4 5HC3 [1] 59:15</p> <hr/> <p style="text-align: center;">6</p> <hr/> <p>6 [24] 3:4 18:1 75:15 88:4 110: 2 148:8 154:3 160:21 209:3, 12 217:9 269:22 272:11 275: 18 283:8 285:4 330:18 343: 14,16 344:8,13 345:21 346: 12,17 6,000 [1] 253:3 6,600 [1] 76:2 6-month [1] 86:4 6.02 [1] 227:9 6.1 [1] 272:6 60 [8] 69:21 75:9 78:18 79:2 104:15 134:6 346:9,17 60s [1] 73:20 63-year-old [2] 118:22 286: 20 64 [2] 163:2 283:19 65 [4] 255:13,14 278:14,15 69 [1] 3:18 6900 [1] 134:20</p> <hr/> <p style="text-align: center;">7</p> <hr/> <p>7 [12] 72:19 95:21 96:16 102:4 110:3 270:22 275:18 285:5</p>	<p>286:3 294:13 315:16,18 7,000 [1] 165:19 7,447 [1] 94:17 7,500 [2] 39:20 40:9 7,855 [1] 97:18 70 [6] 75:9 104:17 123:12 346: 10,10,17 74 [1] 284:21 77 [1] 163:1 77-year-old [2] 118:7 287:1</p> <hr/> <p style="text-align: center;">8</p> <hr/> <p>8 [21] 3:6 83:5,17 88:8 106:18 110:3 117:21 130:16 133:10 162:18 228:11 272:10 277: 20 285:2 294:14 296:5 330: 18 341:19 344:7,8,8 8,000 [1] 41:11 8-fold [1] 82:16 8.4 [2] 75:17 103:10 8.5 [4] 262:14 280:17 281:3,5 8.6 [1] 81:7 8:00 [1] 1:8 80 [5] 66:11 125:5,6 169:9 293:1 800 [1] 156:7 82 [1] 177:22 85 [1] 54:17 8727 [1] 1:10 88 [2] 110:11 280:5</p> <hr/> <p style="text-align: center;">9</p> <hr/> <p>9 [11] 66:8 98:21 110:2 148:8 154:4 271:16 277:19 283:9 290:2,9 292:3 9-24-96 [1] 309:2 9-fold [3] 106:18,22 107:3 9.3 [1] 84:11 9.4 [1] 262:11 90 [4] 71:16 79:5 169:9 258:5 91 [2] 283:14,19 93 [2] 3:20 70:8 96 [1] 308:21 975 [2] 309:9 311:19 99 [2] 42:18 318:21</p> <hr/> <p style="text-align: center;">A</p> <hr/> <p>A [1103] 2:3,9,12,14,16 3:6 5:7, 7,13 7:18 8:12,17 9:2,9,12, 21 10:10,11,14,15,19,22 11:2, 4,8,12,14,15,17,18 12:6,11, 17 13:2,5,16 15:14 16:4,11 17:19,20 18:6,11,12,13,19 19: 11,17,20 20:13 21:13 23:18, 20,21 24:2,3,9,18,19 27:1,11, 12,19,20 28:15,16 29:3,4,11, 11 30:2,3,9,9,18 31:5,13,21 32:4,15,17 33:2,4,4,8,10,11, 21 35:3,5,9,13 36:1,1,6,10 37:13,18,20 38:14 39:2,8,8, 14,21,22 40:4,9,21 41:5,8 42: 3,8,19,20 43:3,20 44:1,2,10, 15,19 45:8,12,18,18,19 46:2, 4,21,22 47:4,6,8,10,13,15,18 48:7 50:14 51:9 52:2,9,16 53: 1,2,5,10,18 54:3,5,20,20 55:7, 19 56:4,4,5,13,15 57:2,7,13 58:2,7,16,17,20 59:12,17 60:</p>	<p>1 61:5,14 62:12,14,17,20 63: 5,8,19 64:4,7,11,13,17,22 65: 4,6 66:1,16 67:3,3 68:4,13, 15 69:18 70:6,6,8,11,12 71: 12,19 72:5,12,19 73:9,11,13 74:4,10,11,11,22,22 75:5,5,8, 11 76:19 77:4,7 78:6,13,19, 20,22 80:11,17,20 81:22 82: 22 83:9 84:1,10 85:20 86:1,2, 4,11,12,14,22 87:3,14,15 88: 3,5,9 89:4,4,6,15,21 90:1,1 91:16,17 92:4,5 94:3 95:3,19, 20,21 96:6,13 97:17 98:8,21, 22 99:3,15,18,22 100:8 101: 19 102:2,9,16 103:1,11,14,19 104:1,3,6 105:4,14,17,22 106: 1,6,11,14,16,19,19,22 107:4, 4,15,19,20,20 108:1,2,18,19 109:15 110:1,9,13,20,21,21 111:13,14,15,16,18,22 112:2, 21 113:3,8,13 114:2,4,20,22, 22 115:3,15,18,19 116:7,13, 22 117:1,6,19,22 118:9,14 119:9,11 120:19,20 121:20, 21,22 122:14 123:17,18,19 124:11,13,13 125:8,9 126:12, 13,15,20,21 127:4,13,18,18, 20,21,22,22 128:1,12,13,14, 19 129:2,8,11 130:1,5,15,15, 21 132:22 133:7 134:3,4,5,16, 21 135:9,13,14,19,20 138:11 139:1,3,12,16 141:4,12,14,15, 19 142:6,7,15 143:3,12,15,16 144:4,6,12,21 145:4,8,17,18, 19 146:7,18 147:13,15 148:2, 6 149:1,4,5,6,14,19,20 150:5, 13 151:12,19 152:3,7,10,18 153:6,12,16,19 154:1,7 155:1, 2,4 156:3,6,10,21,22 158:17 159:11 160:20 161:7 162:10, 11,17,18,19,22 163:22 164:1, 8,13 165:4,11,16,22 166:1,7, 9,12,18 167:6,7,8,15,21 168: 2,19 169:18,22 170:3,4,21 171:1,2,5,13,15,15,22,22 173: 3,7,11,20 174:12,14 175:14 176:14,17 177:20 178:20,22 179:16,22 180:5,12,15,21 181:8,19 183:11,15 184:1,2, 14,16 185:1,20 186:2,4,9,14, 16,16,20 187:2,8,19 188:14 189:13,21 190:3,12 192:8,11 193:3,10,21 195:1,20,21 196: 15,22 197:2,3 198:9,10,21 199:8 200:1,11,17 201:7 202: 1,21,22 203:5 204:2,3,9,12, 19 205:2,11,17,18 208:4,7,8 209:4 210:6,9,12,17,20,21 212:1 213:13,15 214:10,14, 17 216:5 217:9 218:5,8,20,21, 21,22 219:17,22 220:5 222:1, 5,7,16 224:6,9,10,11,17 225: 8,11,19 226:21 227:1,5,17,17, 19 228:10,10,11,15,22 229:4, 9,16 230:2,3,14,22 231:10 232:5,8,15,17 233:3,4 234:8, 17,18 235:2 236:11,20 237:6,</p>
---	--	---	---

7,13,15,19,22 238:3,5,7,8,20 239:1,12,22 240:2,5,6,9,11, 14,19,21,22 241:2,10,13,14, 19,21 242:9,11,12,13,22 243: 4 244:6 246:3,20 247:4,8,16, 17,19,21 248:18 249:20 250: 15,21 251:2 252:6,13,20,21 255:5,10,19 256:6,17 257:3,3, 4,10,17 258:3,11 259:17 260: 3 261:1,6,15 262:16,17,21 263:18,19 264:12,13,14,21 265:3,4,8 266:1,3,3,16,22 267:19 268:3,6,6,21 270:21 271:10 272:5,6 274:2,8,11,15, 17,18,21 275:5,6,12 276:19 277:2,7,11,11 278:4,5,11 279: 1,7,10,12,15,17,20,21 280:1, 6,7,10 281:14,22,22 282:9,13, 21 283:11,13 284:1,6,8,9,17 286:20,22 287:1,3,4,7,9,12, 17,18 288:7 289:2 290:7,15, 17 292:13,15 293:21 294:6,9 295:14,16 297:16,17 298:3,5, 7,17 299:17 300:5,13,14,19 301:1,2,6,11,11,12,12,15,15, 19 302:3,12,13,13,14,16,17, 21,22 303:3,10,14 304:2,4,4, 6,9,16,18 306:1,4,4,9,12,13, 18,20 307:9,22 308:6,14 309: 9,18 310:17 311:10,19,21 312:9 313:12,13,21 314:5,5,8, 18 315:4,6,10 316:9,16 317:4, 5,6,13,17,19,20 318:2,4,5,7, 10,10,12,13,17 319:10,13,13, 16,17,18 320:2,15,17,19,20, 22 321:1,7,8,12 322:15 323: 20 324:4,7,19 325:2,3,14,17 326:2,15 327:2,2,4,9,13,14 328:1,19 330:10,20 331:6,7, 11,11 332:11,13 333:3,13,14 334:1,7,12,19 335:2,6,12 336: 3,12,12,18,20 337:1,3 338:9 339:10,14 340:11,12,14 341: 4,8,8,9,12,14,15,15,16 342:5 343:6,15,16 344:17,20 345: 16 347:2,19 349:4,5,22 350:9, 16,17,20,22 351:11,12,12 352:5,9,10,12 353:13,21 354: 15,15,18,22 355:2,4,14 356:5, 10,11 357:4,9,20 358:9,16 359:1,4,15 360:5,10,20,22 361:1,12,12,22 362:12,19,22 363:4,4,8,11,13,18 364:19,20, 21,22,22 366:3,4,6,11 367:4, 12,16 368:13,16,19,22 369:9, 21 370:8,18,22 371:6,6,19,22 372:1,7,12,15 373:2,6,8,18, 22 374:9,19 375:3,11 376:1,4, 4,9,15,19 377:1,1,4,5,14,22 378:4,11,15 379:2,5,13,19,21 380:17,18,19 381:17,18 382: 12 383:5,11,15,17 385:4,10 a.m [2] 1:8 221:7 A1 [3] 53:13,15 198:14 A1C [12] 86:10,12,19,22 87:20 90:14,16 92:9 253:9 297:7 346:14,15	Abbott [1] 9:17 abdomen [1] 19:10 abdominal [4] 78:5 81:19 91: 19 241:12 abdominally [1] 299:8 aberration [1] 331:12 aberrations [2] 231:12 331: 14 ability [4] 196:19 203:6 234: 19 368:12 able [8] 85:17 97:6 170:11 240:14,15 241:16 312:1 322: 13 abnormal [1] 59:14 abnormality [1] 78:11 about [219] 5:16 10:22 11:10 12:6 16:4,11,22 17:15 18:11 20:14 24:20 25:5 27:1,19 30: 18 31:1,4,10 32:17 33:22 34: 18 35:11 36:5 40:9 46:21,22 47:10,18 49:22 57:4 58:19 63:22,22 65:8,12 66:11 70: 22 98:21 104:3,6,15 106:21 107:1,2 108:11 115:22 117:7 118:12 120:11 121:1 122:22 123:12,14 124:21 125:5,19 137:11 144:6 146:17 149:8 151:13 154:9 155:1 162:16 166:13 171:20 174:12 175:7, 13 176:4,7,12 180:2 183:14, 21 184:3 185:2,5 187:2 189: 21 203:5 212:15 218:14,22 219:5,18 222:11 232:6 234: 13 235:20 236:9 237:10 238: 3 239:14 242:13 243:21 246: 22 257:3 258:1 266:8 269:20 272:22 286:4 288:13,20 295: 14 297:1 298:9,10 304:11 307:22 309:5 312:8,14,18 313:2,5,16 314:22 315:2 318: 19,22 320:19 321:1,12,14 322:1 323:12 324:9,12 325: 13 327:22 329:20,22 330:3,4, 7,8,10,17 331:14 332:6,15,22 333:3 334:14 335:8,12 336:7, 10 337:9 339:2 340:18,19 341:20 342:8,11,16 343:3,15, 16 344:4,7,8,16 345:1,12,21 346:9,10,12,17 347:2 348:6 351:1,4,8 352:15,17 354:9 357:2,9,9,11 359:6 361:2,11, 13,18 362:6 363:1,13,14 364: 14 366:9,21 367:7 368:4,12 371:17 372:15,20,21 373:10, 15,20 374:17 375:17,22 376: 21 377:10 378:5,7,11,12 381: 8,14 382:19 385:7 above [4] 70:6 228:11 291:15, 21 absence [5] 55:18 56:10 208: 14 233:16 357:9 absolute [5] 227:6 293:2 297: 2 343:12 344:9 absolutely [3] 287:5 379:16 382:8 absorbed [1] 296:2 absorption [1] 42:17	abstinent [2] 115:2 322:14 abundant [1] 273:16 acceptable [2] 160:18 379:6 accepting [1] 219:11 access [9] 130:8 141:17 142: 9,18,20 155:1 245:12,20 251: 4 accidental [3] 18:2 20:21 25: 11 accompanied [3] 13:6 253:8 383:18 accordance [3] 38:3 39:10 150:15 according [9] 87:13 119:2,12 124:2 141:15 180:18 262:3 305:4 309:8 accordingly [3] 112:9 129:22 160:9 account [7] 28:2 171:10 179: 13 254:17 314:20 315:1 364: 8 accounted [1] 280:16 accounting [2] 96:2,17 accumulate [1] 220:18 accumulates [1] 270:6 accumulation [3] 42:19 159: 1 198:21 accumulative [1] 72:21 accurate [2] 215:20 266:2 accurately [2] 228:1 348:13 acetylcholine [1] 50:21 acetylcholine [1] 194:18 Achievable [1] 244:19 achieve [5] 80:22 85:17 199: 3 298:18 344:12 achieved [5] 87:9 88:10 161: 3 169:7 244:16 achieves [1] 95:3 acid [2] 62:11 188:4 acknowledge [1] 299:18 across [25] 16:14,18 19:3,19 29:4 32:16 62:5 77:22 81:14 83:16,17,19,21 86:8 100:13 105:3 110:9 146:16 175:12 202:18 204:1,4 205:13 206: 20 257:11 act [8] 23:19,20,22 120:7 188: 9 192:6 193:21 285:3 Acting [6] 5:6 9:3 58:10 61:9 199:21 371:15 Action [24] 3:14 11:15 19:12 37:14 48:13 49:8,11,16 50:2 58:3 64:7 67:4,14 148:18 183:10 186:6 203:6,11 213: 18 215:10 224:10 296:1 304: 8 334:8 actions [4] 60:1 67:6,8,12 activated [3] 219:22 288:1 305:9 activates [1] 192:22 activating [1] 60:9 activation [4] 52:3 61:8 267: 6 269:16 active [34] 21:10 27:16 30:19 35:14 77:9,10 84:17 85:1 89: 20 90:1 108:4 111:21,22 112: 7,8 115:15 126:18 132:16	158:4 189:17 196:22 198:9 200:18 201:11 220:9,13 283: 16 286:17 296:1 316:5,12 339:18 380:13,15 actively [1] 143:12 activities [3] 196:18 198:1 276:7 activity [20] 42:6 54:21,22 56: 13 62:15,17,18 70:14 73:6,15 110:2 187:6 194:15 195:18 197:10 198:7 202:1 203:20 225:22 269:14 acts [4] 57:7 67:10 68:4 101:2 actual [7] 31:3 125:20 164:18 247:13 249:18 302:12 366: 22 actually [38] 20:6 26:10 27:2 33:21 36:11 54:18 124:16 170:16 178:8 231:9 241:19 247:11 274:21 294:4 305:1,2 306:9 309:16,20 315:11,18 316:2,8 322:18 328:2 337:11 341:7 348:16 352:14,18 355: 13 357:4 360:17 362:11 363: 6 370:19 382:18 383:3 acute [4] 60:15,19 61:1 208: 22 ad [1] 376:21 add [2] 288:8 385:6 added [3] 87:8 263:11 265:14 adding [2] 80:15 286:9 addition [19] 60:13 72:16 73: 18 80:14 101:7 102:1 113:12 114:1 127:18 128:7,10 134: 20 168:8 226:12,22 231:8,10 256:8 382:5 additional [27] 12:20 13:9 62: 9 63:12 97:15 100:9 118:11 245:6 246:7 260:11 263:5 268:5 273:2 278:10 293:3 303:3 311:8,9 348:20 356:6, 21 358:13 372:20 373:11 374:1 385:6,7 Additionally [1] 273:21 address [15] 10:5 12:9 19:15 45:11 135:10 157:16 159:19 169:19 170:11 171:7 175:4 220:4 223:14 340:7 381:6 addressed [2] 159:15 219:2 addresses [5] 8:16 126:8 158:22 168:11,13 addressing [3] 41:6 171:9 353:6 adds [1] 285:18 adenosine [3] 53:13 195:12 198:14 adenylate [1] 195:19 adequate [7] 46:19 85:18 208:1 309:3 342:4,19,20 adequately [2] 339:5 362:14 ADHD [1] 34:14 adipocytes [5] 52:10 64:9 88: 16 194:1 326:19 adiponectin [5] 67:19 68:10 88:15,17,19 adiponectin/adipocyte [1] 326:18
---	---	---	--

<p>adipose ^[4] 67:11 189:14 200:22 225:7</p> <p>adiposed ^[1] 64:21</p> <p>adiponectin ^[5] 64:11,14,18,20 65:5</p> <p>adjourn ^[1] 385:20</p> <p>adjourned ^[1] 385:22</p> <p>adjourns ^[1] 221:4</p> <p>adjudicated ^[4] 133:12 309:8 310:22 319:6</p> <p>adjudication ^[3] 133:18 271:7,15</p> <p>adjudicators ^[1] 271:9</p> <p>adjunct ^[1] 43:17</p> <p>adjunctive ^[1] 245:10</p> <p>adjust ^[3] 111:11 115:6 154:11</p> <p>adjusted ^[5] 80:3 81:8 83:16 84:11 87:2</p> <p>adjustment ^[2] 113:9 135:19</p> <p>administered ^[2] 47:12 267:7</p> <p>ADMINISTRATION ^[15] 1:2 29:3,19 36:20 42:9,20 47:9 60:19,21 232:5 270:16 274:20,22 309:5 373:16</p> <p>admit ^[1] 383:6</p> <p>ado ^[1] 185:12</p> <p>adolescents ^[1] 287:21</p> <p>adrenal ^[1] 187:11</p> <p>adult ^[4] 19:5,8 91:15 321:3</p> <p>adults ^[3] 183:20 287:21 319:19</p> <p>advance ^[1] 362:16</p> <p>advanced ^[1] 205:7</p> <p>advantage ^[3] 87:17 178:4 294:5</p> <p>advent ^[1] 196:14</p> <p>adverse ^[136] 12:14 15:5 17:4,6,8,15 20:12,22 28:16 32:12 58:1 79:17 94:3,21 98:6,14 100:6,22 101:3,10 107:9 108:7 125:19 135:6 153:7 154:14 159:10,13 167:10 170:1 171:2 172:20 173:5,6,7 175:17 181:4 182:13 200:3 205:12 208:3 215:9 227:2 247:12 248:13,22 251:21,21 257:9 258:2,13,14 260:5,6,14 261:11,17,19 262:1,13 264:13 265:4 266:3 268:17,19 277:3,8,15 278:4,12 279:16,21 280:6,14,16,21 281:22 288:12,13,20,22 290:9 293:8 294:22 295:10,12,14,18 296:7,8 297:12,16,20 300:7,18 302:9 306:10 307:1,17,22 318:5,8,11,13,15 321:13 328:10 329:4,5 334:12 340:9 343:4,11 344:3 347:21 349:19 350:5 352:11 355:13 358:3 361:17 362:11 363:10 367:2 371:4,10,11,11,18,21 373:4 375:19,20 376:1 377:14 382:6</p> <p>adverse-event ^[5] 28:20 257:16 276:5 277:13 302:12</p> <p>advertising ^[1] 151:8</p>	<p>advice ^[2] 101:13 381:2</p> <p>advise ^[2] 223:3,12</p> <p>Advisors ^[1] 7:2</p> <p>Advisory ^[11] 5:4 13:22 14:9 36:19 46:12 48:11 120:22 138:10 222:19 251:20 352:3</p> <p>Advocacy ^[1] 4:7</p> <p>AE ^[1] 180:14</p> <p>AEs ^[7] 126:2 295:17,17 361:1 371:6 378:5,6</p> <p>affair ^[1] 334:3</p> <p>Affairs ^[1] 37:1</p> <p>affect ^[4] 194:12,22 261:4 276:21</p> <p>affected ^[5] 195:2,4 350:1 351:13,13</p> <p>affecting ^[1] 218:19</p> <p>affinities ^[1] 197:20</p> <p>affinity ^[6] 53:1,2,10,15 203:2 204:3</p> <p>afford ^[1] 242:18</p> <p>afraid ^[1] 350:10</p> <p>African-American ^[1] 63:2</p> <p>African-Americans ^[1] 382:10</p> <p>after ^[31] 17:20 19:2 63:8 69:11 76:18 77:8 80:12 84:17 85:3 88:4 96:10 117:21 118:12 127:13,21 128:1 129:2 130:18 139:6 144:12 166:13 167:6 173:10,14 232:13 258:3,5 284:9 292:11 294:8 365:4</p> <p>afternoon ^[6] 200:13 212:15 222:3 243:10 251:9 380:22</p> <p>afterwards ^[1] 115:4</p> <p>Again ^[74] 13:8,12 32:19 37:20 44:22 58:16 83:14 97:12 114:17 118:7 122:5 123:1 124:11,14 126:20 129:13 133:6 141:20 143:16 146:11 147:10 149:18 150:18 151:15 153:10 154:17,18 155:2,6,20,21 156:13 157:2,5 197:13 213:4 219:3 224:12 227:15 228:4 242:19 255:8 263:16,18 264:7 276:19 277:9 278:5 283:4 285:12 287:10 289:10 292:3 295:13 296:10,13 304:1,12,18 305:6 310:21 318:5,20 336:6,9 338:15 339:2 340:1 344:1 354:5,7 364:1 368:20 373:3</p> <p>against ^[2] 243:1 246:6</p> <p>age ^[9] 62:2 66:5 118:10 255:11,13 278:12,14 307:17 323:10</p> <p>Agency ^[5] 13:13 37:6 46:4 183:16 367:12</p> <p>agenda ^[5] 5:7 8:9,19 9:21 10:14</p> <p>agent ^[8] 134:16 137:10,11 296:1 354:12 368:5 371:15 372:7</p> <p>agents ^[4] 192:7 243:22 245:6 381:21</p> <p>ageusia ^[1] 262:20</p>	<p>aggravated ^[1] 70:18</p> <p>aggregate ^[1] 265:18</p> <p>aggression ^[8] 226:19 227:14 273:19 274:7 314:1 350:15,17 352:16</p> <p>aggressive ^[1] 241:5</p> <p>aggressiveness ^[4] 206:10 207:1 214:7 231:14</p> <p>aging ^[1] 233:14</p> <p>agitation ^[2] 226:20 293:18</p> <p>ago ^[7] 135:3 139:15 230:13 309:9 311:19 327:14 336:18</p> <p>agonism ^[9] 54:13,19 55:7 56:16 57:1,6,14,15 198:6</p> <p>agonist ^[19] 11:1 53:18,20 55:11,11,18,19 56:3,10 58:11 196:17,18,18 197:3,4,5 210:20 238:9 274:9</p> <p>agonists ^[13] 54:4,16,18 55:3,5,5,13,14,20 56:2 197:9 201:18 267:8</p> <p>agree ^[14] 13:16 138:10 234:16 313:8 334:1 349:16 352:12 353:13 354:4 356:1 365:16 367:12,20 379:16</p> <p>agreed ^[6] 46:4 124:3 147:19 148:22 150:16 336:19</p> <p>agreed-upon ^[1] 154:20</p> <p>agreeing ^[1] 10:16</p> <p>agreement ^[4] 141:16 144:3 153:18 367:11</p> <p>agrees ^[1] 344:19</p> <p>ahead ^[4] 36:11 50:22 338:3 368:19</p> <p>air ^[3] 240:19 241:9 337:5</p> <p>Alabama ^[1] 7:7</p> <p>albeit ^[2] 268:22 272:6</p> <p>alcohol ^[2] 94:14 114:12</p> <p>alcoholic ^[2] 129:16 285:8</p> <p>alcoholics ^[1] 256:7</p> <p>alcoholism ^[2] 110:8,13</p> <p>alerted ^[1] 134:1</p> <p>Aleve ^[1] 337:11</p> <p>algorithm ^[2] 11:9 20:2</p> <p>aligned ^[1] 90:4</p> <p>alive ^[2] 66:11,12</p> <p>all ^[152] 8:20 10:3 13:13,16 15:15 16:3,9,18 19:19 20:18,21,22,22 21:8,11 23:5,7 28:3 30:2,4 31:7 32:21 34:13 36:2,4 39:7 40:11 43:22 45:20 60:8 65:12 73:9 75:11 77:15,22 78:1,20 80:2 82:5 91:10 92:15 99:17 102:11,13,16 105:9 107:1 109:8 110:6,7,18 111:9 112:4 113:7 115:12 129:13,21 130:6,8 131:3,4,5,7,17,20,21 132:1 133:1,2,3,5,11,17,17 135:22 139:20 142:14 149:14 152:6 153:13 165:8 175:1 178:20 181:21 184:20 187:2 194:19 200:19 206:7,10,12 212:22 229:5,7 232:14 236:2 238:17 240:7 245:5 250:18,21 254:6,19 257:10 264:14 269:7 271:6,8,22 277:16 278:5 284:15 285:21 286:</p>	<p>15 289:16 292:11 295:9 296:7 299:18 300:6,9 303:11,13 306:9,13 318:16 319:12 320:5 322:15 328:6 329:22 331:4,9 337:4 341:17 347:3,4,9,15 348:9 353:16 355:17 361:2,10,22 362:20 364:8 369:4 374:21 377:4 381:14 385:13</p> <p>allegedly ^[1] 117:13</p> <p>allocation ^[1] 230:8</p> <p>allosteric ^[1] 198:8</p> <p>allow ^[3] 30:12 37:9 381:8</p> <p>allowed ^[2] 129:10 136:21</p> <p>allude ^[1] 218:13</p> <p>almost ^[9] 40:17 94:16 99:17 226:18 242:13 277:22 296:19 300:17 377:21</p> <p>alone ^[11] 82:13 89:8 90:6 92:13 108:11 169:14 215:1 253:2 263:8 300:20 366:7</p> <p>along ^[6] 42:9 153:21 250:21 252:21 374:14 378:2</p> <p>alopecia ^[1] 183:5</p> <p>alpha ^[1] 60:6</p> <p>already ^[13] 9:20 82:14 108:18 151:2 180:5 190:15 194:8 341:22 364:1,18 372:12,19 381:12</p> <p>also ^[127] 9:10 10:11,17 26:16 29:10 32:19 38:7,12,17,19 39:6,11 41:4,17 42:13 44:12 47:18,19 48:20 52:4 63:2 67:10 70:3 72:10,12 73:12 76:10,13 77:7 86:18 87:10 88:11 90:15 91:5 95:18 101:7 120:16 122:19 124:8 129:2 130:1 140:15 141:6,12 142:1,12 143:11,21 147:4 149:13 150:16 153:4 155:1 156:2,20 157:9 158:8 159:5 161:6 175:20 177:1 178:21 179:2 183:1 187:7 188:17 189:5,13,16 191:2,14 192:16 197:11,16 198:14 199:14 202:13 203:12 207:2 210:17 217:13 218:20 226:19 227:11 231:17 233:12 236:1 255:9 261:5 273:10 274:7,10 280:4,5 282:20 290:4 302:17 308:12,14 310:12 312:17 323:17 328:1 330:8 331:17 334:7 344:20 346:13 350:19 351:1,1 352:17 360:8,14 361:13,18 362:1,6 363:18 364:6,7,9 366:14 368:1,7 378:18 384:22</p> <p>alteration ^[1] 276:21</p> <p>alterations ^[7] 99:7 104:1,22 105:8,14 106:13 147:1</p> <p>altered ^[1] 276:21</p> <p>alternative ^[3] 27:13 28:1 30:5</p> <p>Although ^[19] 112:10 135:17 182:15 205:3 206:22 207:8 219:9 233:14 266:20 273:10 297:20 304:22 305:2 311:8 312:14 315:17 353:10 354:9 361:14</p>
--	--	---	--

<p>always ^[10] 6:5 30:18 33:13 73:14 115:5,19 122:7 135:18 146:20 376:12 am ^[98] 5:5,6,9 6:5,6,8,10,12, 14,17 7:12,12,18,22 15:10,15 16:4 17:14 23:10 36:21,21 93:11 105:12 106:9 156:4 216:6 219:7 224:1 238:2,18 239:3,16 241:7 243:11 265: 22 293:20 300:19 303:6 304: 15 307:13 308:4,4 309:2 310: 21 311:16 312:8,13,17 313:2 320:9 323:1,4,6 325:13 327: 12 328:22 329:14,17 331:18 332:15 333:21 334:21 335: 11,12 336:9,10 337:18,20 338:8 339:3 340:10,18 341:7 342:11,16 343:1,3 347:2,18 349:10 351:1 352:15 359:3,5, 6,15 360:6,20 362:6 366:11 367:19 368:4,9,11 370:11,12, 21 385:4 amazing ^[2] 237:2 370:14 ameliorated ^[1] 331:20 amelioration ^[1] 59:19 America ^[17] 39:1,2 76:6 77: 7,18 78:1 80:5 84:9,15 96:5 115:4 118:21 255:12,16 259: 19 284:7 286:20 American ^[5] 25:6 76:3 82:11 144:3 158:9 Americans ^[2] 63:2 161:2 amidohydrolases ^[1] 43:1 aminohydrolase ^[1] 62:12 amnesia ^[3] 125:10 264:6 305:19 among ^[10] 28:3 107:9 113:5 186:22 189:19 196:10 244: 16 261:19 280:1,18 Amongst ^[1] 231:2 amount ^[13] 30:22 31:9 58:5, 8 63:20 65:21 236:1,22 240: 8 326:4 342:17 360:4 361:13 amphetamines ^[1] 73:19 amplification ^[1] 107:2 Amy ^[5] 2:26 4:15 6:12 12:1 222:6 amygdala ^[2] 51:20 225:4 an ^[247] 5:9 9:21 18:14 19:8,8 20:11 24:20 25:20 26:4 28: 11 31:3 33:8 34:15 35:14 41: 11 43:17 44:3 45:3,7,14 46: 16 49:16,17 50:19 52:20 53: 14,18,20 54:16,19 55:10,15 56:2,3,10 57:10,14,22 58:10, 12 60:18 62:22 63:13,13 64: 2,9 65:16,22 66:16 67:22 70: 2 71:9 79:8 82:16 83:5 84:7 85:5 87:8 88:19 89:12 90:4 91:5,19 95:14 98:7 100:18, 21 107:2 108:4 109:13 111: 22 112:8 114:6 115:15,17 117:2 118:15 119:20 121:15 122:2,21 123:22 125:22 128: 3 131:16 134:19 135:17 136: 17,22 137:11 141:11,17 142: 4 143:21 144:2 145:13,16</p>	<p>148:7,17 152:20 153:17 154: 7,19 155:16 156:19 158:14, 22 159:12 160:18 162:13,21 164:4,10,14 165:6 166:8,8,9 167:3,21 168:4,7,17 169:21 172:5 178:4 180:14,16 181:4, 18 183:7 185:10 186:6 188:4, 9 192:20 196:18,22 197:1,4, 10 199:21 202:1,9,12,13,16 207:13,22 208:14 209:20 210:10 215:20 222:21 225: 16 227:2 228:9 229:9 231:18, 18 232:18 233:11 236:1,18, 22 238:8 239:1 240:7 242:7 254:20 258:8 260:2 266:20, 21 268:6 269:14 273:17 275: 4,13 277:8,14,22 279:19 281: 1,7,11,13,21 286:10,21 287: 14,22 288:3,8,16,18 289:21 290:5 292:20,22 293:2,11 295:21 297:11,14,15,18 299: 3 300:4,17 302:2,12 306:4 307:6 309:3 311:8,9 313:8 314:10 316:12 317:2 319:21 320:21,22 321:3 326:8,16 328:18 332:3 338:4 341:13 345:3 348:20 354:10 357:6, 16 360:21 373:5 375:11,16 376:3 377:21 379:6 380:21 383:1,2 385:14 analgesia ^[1] 59:19 analgesic ^[1] 60:21 analogies ^[1] 83:10 analogy ^[1] 60:1 analyses ^[28] 28:4,7,17 32:16, 21 95:7 96:16 97:7 120:14, 14 131:6 134:9 136:16 218:3 254:19 255:10 256:14 257: 11 258:8 260:10 271:7 277: 12 278:10 284:7,15,21 355:3, 18 Analysis ^[83] 15:6 18:14 22:2, 2,20 25:14 26:4,13,16 28:11 46:1 80:2,21 81:21 89:1,14 95:1 96:18 97:1 109:13,21 111:18 112:2,18 114:1,4,10, 15,16 115:14 131:2,11 132: 11,19 133:1 145:11 163:12 170:18 172:17,21 173:21 254:16,21 257:14 259:4 260: 9 262:8 263:4 265:15 271:22 272:1 275:16 283:13,13 284: 4,11 285:19,22 286:9 297:4 300:6,20 308:3,8 310:6,12 316:7,9,21 317:1,22 321:8 324:2 325:5 348:13 355:5 360:7,10,11,20 366:15 367: 13 373:6 analyze ^[3] 172:18 271:8 312: 1 analyzed ^[6] 95:18 129:13 130:13 258:12 311:13 367:9 anandamide ^[10] 50:18 56: 20 61:16 62:3,13 188:1 196: 6 273:22 274:2 312:22 AND ^[1521] 1:1,2,3 3:16 4:8,14, 16 5:3,4,5,7 6:2,9,11,16 7:3,</p>	<p>13,21 8:16,20,21 9:6,17,18 10:1,10,11,18,19 11:3,6,8,11, 16,22 12:3,6,8,13,14,14,15, 20 13:3,5,9,12,14,15,21 14:5, 9,11,16 15:11,16,19,20 16:2, 3,10,12,14,18,21 17:1,7,13 18:2,13,21,22 19:5,6,11,17, 19,20,22 20:11,13,17,21,22 21:3,11,11,14,20 22:3,5,14, 17 23:4,4,5,7,13 24:2,11,22 25:1,12,21 26:6,14 27:1,12, 21 28:3,10,12,17,18 29:7,8, 12,12,12,16,19,21 30:1,1,4, 22 31:5,11 32:4,10,13,17 34: 1,1,17 35:16,19 36:2,3,6,20, 20 37:1,1,5,8,16 38:3,6,10,13, 17 39:2,7,8,9,22 40:9,20 41: 15,16 42:3,4,20 43:1,12,17 44:1,2,5,7,22 45:10,15,20,21 46:4,10,11 48:8,8,10,17,20, 22 49:3,4,5,7,15,18 50:3,4,7, 9,13,16,17,18,20,21,22 51:2, 6,6,21 52:1,5,11,14,18,19 53: 2,6,8,9,21 54:12 55:7,17 56: 20 57:18,20 59:1,6,7,14,20 60:2 61:6,9,10,16 62:2,3,5, 10,16 63:15,21 64:16,20,21 65:6 66:1,6,18 67:1,7,7,12, 13,14,18 68:1,7,10,13,17 69: 2,5,7,13,16,21 70:4,5,8,14,19 71:11,13,16,20 72:12,13 73:4, 5,6,9,15,19 74:3,6,7,11,21 75: 10,12,13,14,16,19 76:3,3,4,6, 7,17,19 77:2,18,19 78:5,9,16, 19 79:3,11,17,21 80:4,5,9 81: 8,8,12,12,14,14,17 82:11,13, 22 83:1,6,10,21 84:3,8,12 86: 2,5,10,21 87:20,22 88:8,16, 21 89:2,4,7,12,20,20 91:8,16 92:4,6,9,10,20 93:4,10,13,15, 18,18 94:1,2,4,10,14 95:4,5,9, 9,14,21 96:1,14,19 97:2 98:4, 4,8,16,18 99:1,6,7,12,14,19 100:7,10,12,13,14,18,18 101: 2,4,6,11,13 102:3,7,10,12,18, 19,20,21 103:1,9,14,22 104:7, 9,12 105:6,20 106:14 107:3,9, 12,14,15,16 108:9,10 109:2, 13,14,15 110:2,2,3,7,8,11,13, 14 112:3,6,7,8,12,15 113:1,3, 14,15,20 114:7,9,12,13,14,22 115:15 116:13 117:4,5,10,12 118:1,4,11,13,17,18 119:3,8, 11 120:2,4,11,15 121:1,3,5,9, 13,15,16,16,22 122:4,12,15, 18 123:1,4,8,16,18,19 124:2, 4,7 125:4,14,16 126:13,17,22 127:6,15,20 128:4,8,18 129:2, 6,16,19,22 130:4,6,9,13,14, 18,22 131:1,7,13,18,19,20 132:3,5,6,14,15,17 133:13 134:5,15 135:4,8,21 136:9,12 137:1,16,21 138:7,11,12,14, 15,20 139:2,3,6,13,18,21 140: 13,17,17,21 141:6,11,16,18, 20,22 142:4,11 143:2,11 144: 1,2,10,16 145:6,8,15,19 146:</p>	<p>1,5,9,10,13,20,22 147:3,4,6,6, 12,12,16 148:3,8,10,15,16 149:2,5,7,9 150:4,4,17 151: 10,15,15,20 152:1,2,8,10,15, 22 153:4,6,10,17,18 154:3,4, 4,11,13,17 155:7,11,13,18,20 156:9,19 157:6,13,14,16,16, 22 158:4,12,15 159:1,9,12,18, 19,20 160:1,2,6,10,12,18 161: 1,7,10,13,18,18 162:8,15,18, 22 163:2,6,8,15,21 164:1,3,5, 7,9,20 165:7,10,12,19 166:1, 2,3,3,14,15,20,22 167:2,9,14, 15,16 168:3,4,9,12,13,21,22 169:8,13,16,22 170:4,9,22 171:4,9,15,15 172:1,4,5,13 173:20 174:3,12,18,22 175:3, 4,7,7,9,12,13,18,20 176:2 177:12 178:6,7,12 179:6,8,8, 15 180:21 181:5,19 182:6,21 183:5,11,18,19 184:1,5,16,17 185:6,8,16 186:6,9,17,21 187: 4,9,11,16 188:1,3,7,10,16,22 22 189:5,13,13,15,18,20 190: 1,2,4,14,17,18 191:1,4,13,15, 17,19,22 192:4,7,9,15,21 193: 4,5,18 194:1,5,7,10 195:3,12, 14,19 196:2,6,9,17 197:3,4,6, 15 198:7,19 199:9 200:2,6,10, 14,19 201:1,3,5,9,9,15 202:1, 4,5,9,13,16,20,22 203:1,4,6,7, 10,22 204:3,13,15,16,17,22 205:7,16,18,22 206:6,10,14, 22 207:1,13,17 208:2,10,15, 20 209:17 210:8,9,14,16 211: 13,14 212:4,21 213:3,7,16 214:4,5 215:1,2,7,10,11 217: 10,18 218:6,18,21 219:18,19, 20 220:1,5 222:5,13,16,17 223:5 224:6,16,17,18 225:1,2, 4,5,8,14 226:3,4,4,8,14,18,19 227:5,13,16,20 228:5,21 229: 7,13,19,21 230:1,3,8,10,11, 20 231:3,7,8,13,17,22 232:3, 7 233:4,21 234:1,5,13,14,16 235:1,2,10,16,18 236:8,9,15 237:3,5,9,12,18,20,21 238:3, 4,10,21 239:3,8,11 240:5,7, 17 241:1,6,10,19,21,21 242: 10,15,16,17,17 243:1,3,4,15, 18 244:1,3,4,7,11,12,14,18 245:4,10,19,20 246:3,4,6,11, 20 247:5,10,14 248:8 250:9 251:8,10,22 252:1,13 253:3,6, 9,14,15 254:3,7,17,20 255:2, 9,12,14,17,19 256:1,8,13,15, 22 257:9,16 258:2,8,14,20 259:1,8,17,19,21 260:2,3,6,6, 9,16,20 261:3,4,7,12 262:4, 16,19,21 263:4,15,16,17 264: 6,9 265:1,7,12 266:11 267:10, 13,14,18 268:1,4,9,11,12,16, 19 269:11,13,18,22,22 270:3, 17 271:2,17,22 272:4,12,13, 17,18 273:6,15,19 274:1,6,7, 11 275:14,22 276:6,10,12,14, 15,16,17,18,20,20,21 277:12,</p>
---	---	---	--

20,21 278:13,14,16,18,18 279:2,3,13,20 280:4,8 281:4, 15,22 282:3,4,4,5,9,15 283:7, 8,12,21 284:7,16 285:1,4,5,7, 8,9 286:5,15 287:1,6,9,15,20, 21 288:1,5,7,8,20 289:4,5,11, 13,14,15,17,18 290:3,6,10,17 291:2,7,15,21 292:6,14 293:1, 5,13,18 294:3,8,9,11,15,18, 20 295:5,7,13,15,20 296:5,19 297:5,7,7,8,13,18,21,22 298: 1,3,5,6,8,10,12,14,20 299:7, 22 300:18,21,22 301:5,21 302:17 303:8,11,12,17,21 304:21 305:6,11,13 307:2,6,9, 17 308:4,10 309:1,2,16 310:6, 13,14,15,18,22 311:5,12,21 312:10,18,22 313:14,17,19, 22 314:5,11,18,21 315:1,12, 13,14,15 316:1,1,2,3,5,8 317: 4,6,10,18,22 318:3,3,11,21, 22 319:3,6,16 320:12,14,18 321:8,12 322:8,11 323:19 324:2,7,22 325:5,8,21 326:9, 14 327:2,4,7,9,15,22 328:2, 11,16,20 329:1,3,4,5,6,9,12, 20,21,22 330:5,6,15,18,21 331:7,19,20 332:2,3,3,9,10, 12 333:9,10,18,22 334:3,8,9, 9,17,18 335:3 336:2,2,3,10, 11,13 337:2,4,5,5,6 338:5,7,9, 15,18,21 339:4,6,6 340:9 341: 7 343:10,14,15,17 344:3,5,15, 20 345:13,14,14,20,20 346:8, 11,17 347:10 348:9 349:8,20 350:5,6,11,15,17 351:5,11,12, 13 352:17,21,22 353:6,7,11, 15,19 354:12,12,16 355:8,18 357:6,22 358:5,6,7 359:6,12 360:5,7,13,16 361:10,16 362: 1,8,13,19,21 363:7,11,15 364: 6,17,19 365:5,8,8,12,13,13, 16 366:1,2,10,12,22 367:2,3, 9,10,11,22 368:1,3,7,10,15, 19 369:14,18,19,20,22 370:3, 5,7,11,16 371:5,9,13,19,20, 21 372:4,12,19 373:4,5,14,16, 17 374:8,12,19,20 375:6,13, 18,21 376:7,16,16,22 377:3,3, 4,5,20 378:2,22 379:1,2,15 380:4,17,19,21 381:1,6,6,13, 18,21 382:1,2,14,18 383:1,2, 8,12,16,18 385:1,10,15,17 and/or [5] 47:6,14 137:20 147: 14 273:9 anecdotal [2] 35:2 373:22 anger [1] 274:7 angina [2] 302:18,20 angiotensin [1] 164:11 anhedonia [1] 276:16 animal [40] 58:20 61:1 65:11 164:3 198:17 200:16 202:18 203:4,8,9 206:13 208:5,13 211:15 212:13 213:4,22 214: 5,20 217:6 219:5,5,8 222:10 225:17 226:19 227:15 230: 11,14,18 232:22 234:22 247:	19 248:21 249:1,13,22 250:7 360:3 364:15 animals [17] 58:19 59:1 66:2 199:19 200:4 206:14 207:10 208:2,10,15 209:20 211:7 215:19 216:22 248:13 250:4 326:13 announce [1] 383:7 announcement [1] 8:15 annual [1] 128:18 annually [1] 71:15 anonymized [1] 109:4 anorexics [1] 237:4 anorexin [1] 194:19 anosmia [1] 262:20 another [17] 60:13 81:21 107: 12,20 134:16 137:10 169:11 177:3 182:9 183:6 205:5 208: 16 229:15 281:10 309:1 322: 21 379:14 answer [11] 13:8 121:8 132:6 176:9 237:17 299:13 301:8 335:17 338:16 345:18 369:6 answered [2] 150:7 180:5 answers [3] 30:7,13 35:17 antagonism [9] 54:13 55:10 56:22 57:15 58:14 198:13 211:12 213:15 233:18 antagonist [20] 42:4 51:17 52:17,21 54:3 55:17,19 56:2 57:8 58:18 68:4,15 190:7 196:15 197:3 199:22 204:2 214:11 220:6 274:8 antagonist/inverse [1] 11:1 antagonists [4] 54:7,11,18 211:20 antagonize [1] 60:8 antagonized [1] 199:15 antagonizes [1] 207:15 antagonizing [2] 60:10 232: 11 anti-anxiety [1] 202:12 anti-convulsant [3] 202:2 211:9 269:10 anti-depressant [13] 229:10 275:5 281:2,11 287:20 288:1, 4,9,19 290:18 357:6 379:1,14 anti-depressants [11] 229: 13 239:18 273:9 275:1 357:4 378:15,20 379:8 380:6,7,13 anti-depression [1] 229:6 anti-epileptic [4] 47:22 48:5 129:7 147:17 anti-epileptics [1] 152:22 anti-orexigenic [1] 202:16 antiandrogenic [1] 88:21 anticipated [4] 41:11 43:7 212:13 331:8 anticonvulsant [2] 207:17 272:16 anticonvulsants [1] 19:4 anticonvulsive [1] 207:12 antidepressant [17] 17:13 22:3 25:14 26:4 27:7 47:17 102:13 103:3 104:17 108:5 139:17 147:17 180:15,22 181:22 183:8 227:2	antidepressant-like [1] 295: 22 antidepressants [10] 19:4 109:17 150:22 152:22 153: 13 180:11 181:4 183:18,20 184:4 antidiabetic [3] 81:3 88:9,21 antiepileptic [1] 140:12 antiepileptics [1] 153:13 antiproliferation [1] 226:5 antipsychotics [2] 312:12 314:4 anxiety [46] 99:6 101:7 102:3, 14 106:15 119:3 122:19 123: 1,7 166:1,2,20 167:15 200:6 202:15 207:1 213:3 214:6 226:17 227:8 228:5 273:6,14 274:6 276:12,13 277:17 279: 3 281:14 282:3 288:3 289:5 291:6 293:16 297:13 305:11, 13 312:18,19 350:7,9,16 352: 13 361:6 377:20 378:1 Anxiety-related [2] 122:18 304:8 anxiolytic [2] 281:1,7 anxiolytics [2] 123:13 273:9 anxious [3] 5:16 154:22 351: 3 any [84] 9:6,20 10:5,6 15:21 17:5 20:7 21:8,8,11 23:22 31: 1,5,10 33:18 34:3,9,20 47:6 52:20 53:10 64:22 80:22 85: 8 90:9 101:18 108:17 115:4 129:19,19 138:6 148:16 151: 7 154:10,12 168:17 180:20 214:2 216:16 218:7,14 219:5, 8,21 223:4,12 224:7 235:13 236:19,21 243:21 249:8 250: 10 270:14 271:15 274:14 289:17 294:22 296:3 301:7,8 302:5 304:11 305:11,22 306: 19 313:11 314:11 317:9 319: 8 322:22 332:15 333:21 335: 6,14 339:20 341:2 353:1 360: 19 369:20 373:9 374:22 375: 22 383:4 anybody [4] 237:21 249:8 306:1 385:5 anybody's [1] 295:1 anyone [2] 316:7 333:16 anything [10] 34:4 221:1 235: 13 236:12 238:19 291:20 321:22 342:7,10 357:14 anytime [1] 20:11 anyway [3] 242:5 308:18 361: 1 anywhere [1] 240:9 aphasia [1] 266:10 aphonia [1] 263:16 apnea [5] 70:18 72:11 159:4 161:7 244:10 apologize [2] 248:19 249:9 Apovian [5] 4:10 243:7,9,10, 11 apparent [4] 19:7 66:10 119: 2 368:2 Apparently [6] 183:9 191:18	266:20 321:15 332:21 361: 14 appear [8] 113:3 138:3 244: 21 260:17 265:3 297:21 305: 6 336:15 appearance [1] 8:18 appeared [1] 341:3 appears [12] 56:22 178:3 210: 12 211:9 213:19 215:18 219: 19 265:15 278:13 309:12 338:9 354:10 appetite [4] 187:4 191:5 200: 10 366:7 applaud [2] 246:1,2 Applause [1] 14:14 application [6] 43:13 46:3 58: 7 95:4 205:6 251:14 applications [1] 211:22 applied [6] 26:6 44:21 54:5 58:13,15 90:9 apply [3] 19:17 169:3 368:10 appreciate [8] 36:6 59:10 60: 9 307:4 329:11 353:10 354: 14 361:8 appreciation [2] 14:8 174:4 approach [16] 19:22 21:8 45: 10 80:2 98:9 109:16 111:13, 15 115:17 129:18 254:22 255:2,2 276:4 348:17 377:14 approached [1] 338:6 approaches [3] 114:15 141: 4 180:18 appropriate [16] 47:13,20 91: 13 115:9 137:13 138:15 147: 12 148:18 152:3 155:12,13, 14 157:4 167:22 168:2,5 appropriately [3] 30:1 147:7 371:17 appropriately-trained [1] 155:10 appropriateness [1] 155:3 approvable [2] 45:7,12 approval [12] 44:4 135:2 157: 15 234:18 243:17,22 294:16, 21 314:14 323:10 328:19,21 approve [3] 43:21 241:6,8 approved [24] 13:3 40:14 43: 11,15,22 71:14 73:19,22 137: 11 144:9 153:7 224:16 229: 12 235:5 293:10 294:7,9,17, 18 335:15 337:10 339:13 376:15 383:16 approving [1] 294:6 approximate [3] 281:21 297: 11,14 approximately [23] 40:18,22 41:10,20 42:15,18 43:3 63: 17 97:18 98:22 99:3 103:11, 14 112:21 124:11 144:19 156:5 198:21 228:7 253:1 256:21 268:4 309:21 April [3] 43:14 45:4 127:9 apt [2] 288:1 289:9 arachidonic [1] 188:4 arbitrary [1] 31:20 are [489] 5:8,15,16 9:22 10:9, 21 11:6 13:17,18 14:2 16:10,
---	--	---	---

21,21 17:11,13 18:11,19 19:6 21:9,12 22:1,4 23:3,5 24:5,8 25:5 26:1 27:2,16 28:17,20 31:8,13 32:21 33:12 34:5,9, 11,14,19 35:8,16 36:10,10,11 37:3 38:21 41:12,15,16 42: 21 43:7 45:3 46:2,11 47:19 48:1,3,4,14 50:22 51:2,19 52: 13 53:7 54:16,18 59:8,10,12, 18,18 60:14,18 61:17,21 62:2, 4 64:15 65:11 66:4 69:21 70: 4,5,16,17,20,22 71:3 72:3 73: 2,17,20 77:13 79:20 82:6,15 83:2 86:8,10 90:3,12,15 93: 19 97:11,16,21 98:14 100:18 105:9 106:12 107:19 108:16 111:3,3 113:2 114:14 117:1, 13 120:2,5 121:13 122:12 123:1,2 125:7 127:14 131:16 132:17 133:20 135:16 136: 20,22 137:5 138:20 139:17, 18,18,22 140:9 141:4,8,13,18 142:5 143:12,13 144:14 145: 2,15,21,21 146:3,13,15 147:9, 9,11,13 148:9 149:17,19 150: 7,11,13 151:2,10,16 152:10, 21 153:1,7,7 155:18 159:9 161:21,22 163:20 164:18,22 165:2 166:3 172:6,7,21 174: 3 175:11 177:7,11 179:5,12, 14,18 180:11 181:13 184:7, 21 185:2,3 186:22 187:15 188:2,3,6,7,10,13,17,18,22 189:2,4,9,11,16 190:18 191:2, 4,14,15 192:15,16 193:3,7 194:19 195:1,2 196:1,2,6 197:9,17,22 199:4,19 200:2,3, 15 201:1 202:18 203:3,9,12 204:1 206:7,8 209:3,3,7,8,9 210:19 211:1,20 212:3,12,22 214:2 215:1,10,10,18 216:2,3, 3,18,19 217:2,5,9 219:4,9,11, 19 220:1 223:20 224:21 226: 10,15 227:4,6 229:1,10 231:8, 22 233:6,6 234:6,14 235:18, 18 236:4,10,10,14,16 239:10, 16,18 240:6,12,13,13,14 241: 4 242:2,22,22 243:19 244:3,5 245:2,4,6,7,11,21 246:7,19 249:3,20 250:2,17 251:5,19 254:5 257:4 258:6 261:5,22 262:2 263:11 265:18,18 273: 13,16 278:3 281:12 286:3 287:11,22 288:1 291:20 293: 15 294:2,20,20,22 295:1,9,14 296:7,10 297:8,9 298:4,5 299:9,15 300:8 302:16,20 303:14,16,18 307:2,7,10,21 308:5 309:5 310:18 312:3 313:15,15,16 314:2,3 319:2,7, 22 321:1 323:17 325:22 327: 8 328:8,9,18 329:21 330:3 331:2,13,19 332:20,22 333:7, 12,13,17,20 334:10,13 336: 13 337:21 338:12 339:7 340: 1,20,21 341:10,11 342:9,10 343:18 347:4,6,14,20 348:14	349:19 350:2,12,22 351:6 352:22,22 353:5 356:7,14,14, 16 357:16 358:4,5,5 359:1 360:14 361:6,14,19 362:7,8, 20,22 363:5,6,7,12,15,17,20 364:18 365:21 366:21 368:2, 19 369:1,9,12 371:6,7,9,15, 19,19 373:4,4,7 374:6,21,21 377:7 378:6,14,14 380:5 381: 1,12,13,13 382:4,7,22 383:5 385:1,15,16,19 area [13] 48:12 184:16 208:7 231:2 253:18 273:17 291:20 331:7 351:9 356:20 377:19, 20 385:14 areas [8] 29:17 32:5 235:2 258:12 261:3 262:3 357:21 381:9 aren't [1] 360:19 argue [4] 203:12 349:22 350: 1 376:13 arise [1] 233:2 arisen [1] 230:6 arm [11] 21:11 111:14,17,19 116:2 257:18 258:3 277:11 286:6 324:21 359:12 armamentarium [2] 168:8 245:8 arms [1] 176:3 Aronne [8] 3:24 37:22 157:20 158:3,5,8,10,12 Aronne's [1] 246:2 around [15] 5:11,21 18:7,10 20:19 33:17 75:15 105:13,22 291:21 294:13,16 329:9 336: 2 385:5 array [4] 261:15 262:1 263:20 264:7 arrest [1] 183:3 Arrone's [1] 348:16 art [1] 239:1 artery [1] 166:10 articulate [1] 97:5 articulates [1] 36:1 artificial [1] 56:3 artificially [1] 228:17 as [462] 8:9 9:2,12 10:17,21 11:2,4 12:22 13:20 14:15 15: 10 16:5,5 17:9,12 19:7 20:2 21:1 22:7 23:16,20 27:5,20 29:17 30:17 31:17 32:5 35:6, 22 38:16 39:19 40:13,19,19 41:4,19 42:2,14,22 43:5,10, 16,17,20 44:3,8,13,14,21,21 45:15,16,21,22 46:1,1,17,17, 18 50:12,16,16 51:2,14 52:14, 21 53:6 55:6,6 56:1 57:7,9 58:10,17 59:20 60:17 61:15 62:12 63:18,20 65:22 66:1 68:4 69:12 70:6,18 71:7,12, 19 72:17 73:5,22 75:2,5,5,5, 6,15,17 77:1 78:5,6 79:4,15 80:17 81:20 82:10,17,21 83: 4,15,22 84:9,20 85:8,19 86:2, 14 87:4,5,14 88:14,18 89:21 90:2,11,13,17 92:5,5 93:19 94:10 95:10,16,19,20,21 96:5,	9 97:14,20 98:6 99:7,11 100: 9,14 101:4 105:9,18,18 107: 18,20,21 108:13,21 109:7,8, 14,21 110:1,2,3 111:7,13,18, 20 112:4,8 113:7,9,11 115:8, 10,14 116:7,7,22 117:1,2,9 119:16 120:3,10 121:14,14 124:1,5,10 125:9 126:6 127: 13,15 129:16,22 131:8,13 132:13 138:9,20,20 139:1,15 140:9,21 141:2 142:10,21,21 143:5,5 144:8,18 145:2 146: 18 147:20,21 148:9,12,15,15 150:11 151:19 152:12,12 153:5,5,14,15,20 154:7,20,20 155:14 156:2,14 157:7,14,15 161:19,20 162:10,11,11 164: 3 165:2 167:3,15,15,19 168:7, 17 175:12 176:16,21 177:8, 12 179:1 180:13,17 181:18 183:3,7,16,19 187:3,10,10,18 188:22 191:1,1,9 192:6 193: 15,16,16,17,18,20 195:2,2,7, 16,17,20,20 196:4,4,5,15,17, 18,19 197:8,11 198:12 199: 21 201:2 204:20,20 206:15 208:4,12 212:9 213:4,15 225: 20 226:16 227:12,22 230:10, 14 231:14,18 232:15 233:2,7 234:4 237:21 240:1 241:13 243:14,14 244:20,20 245:9, 15,17,21 246:1,12,12 247:11, 19 248:12,21 251:2 252:1 253:4,6 254:7 256:6,11,18 257:18 258:8,18 260:2,5 261: 1 262:8,12 263:13 264:5,17, 20 265:11 266:1,8,12 268:13 271:9,18 272:2,20,20 273:14 274:16 275:21 276:13 277:8, 13 279:5 280:20,22 284:13, 17,17 285:14,17 286:6 287:3 288:15 289:11,16 290:6,8 291:6 293:11 295:8,20 297: 22 298:16 300:15 303:13 304:5 310:6,10,14,15,16,17 311:5 312:4,20 315:17 319:2, 22 320:8,18,21 321:2 322:11 325:7,7 326:4 327:8,8 328: 18 331:2 332:19 333:22 336: 14 337:8,9,14 341:15 344:10 345:9,10,21,22 351:7,7,16 352:7,17 357:18,18 360:4 362:6 364:21 368:7,10,13 369:17,18 370:7,7,11,11,15 372:10 374:12,14,15 376:1 377:9 381:19,19 385:11,11 ascertain [1] 271:10 ascertainment [9] 27:14 30: 6 287:17,17 289:21 290:13, 22 361:9 372:16 ask [28] 10:4 20:21 31:1,4,10 33:17 34:8,22 121:9 149:8, 18,20 172:12 173:11 179:11 219:16 293:20 294:8 303:2 318:19,22 321:11 358:16 372:4 374:12 375:17 383:11 385:5	asked [12] 9:11 20:8 37:6 46: 4 144:14 185:20 223:17 269: 4 282:18 327:6 335:12 371: 17 asking [5] 12:8,17 34:11 184: 19 355:7 aspect [1] 181:10 assess [9] 22:8 27:6 68:18 101:20 136:8 140:18 146:2 182:2 380:2 assessed [3] 131:9,13 200: 16 assesses [2] 29:21 30:1 assessment [20] 11:9 20:2 32:14,19 33:20 102:9,20 114: 8 124:6 134:15 143:19 153:5 155:16 156:19 171:11 173:2 215:21 256:5,10 282:21 assessments [2] 142:19 160: 11 assign [1] 304:15 assigned [2] 283:17 304:13 assigning [2] 258:2 302:9 associated [41] 21:13 24:18 68:7 70:5 72:6 99:13 102:18 113:8,18 122:8 135:18 140: 10 141:1 146:22 147:2 159:8 161:10 162:18 163:15 165: 22 169:16 182:13 185:22 190:1 202:13 213:19,19 214: 4 245:4,14 248:10 258:9 281: 21 297:6,10 304:7 313:9 332: 2 346:16 348:18 350:11 Association [16] 27:7,9,10 62:22 164:5 178:13 211:11 279:1 287:15,16,20 292:2,6 305:11 345:17 358:6 associations [1] 354:12 assume [5] 180:13 238:6 290: 2,5 360:12 assumed [1] 352:5 assuming [1] 240:12 asthenia [1] 293:18 asthmatic [1] 166:9 astrocytoma [1] 341:13 at [288] 5:14 6:21 7:5,9,14,17, 19 8:5,10,11,18 13:6 14:22 23:14,19 28:15 29:22 33:22 39:14,21 40:4 41:3 46:8 47:4 49:4 56:4 57:8 58:1,21 61:6 62:14,18 63:21 64:14,16 65: 12,12 66:3,8 68:3 79:5,6 80: 3,17 81:21 82:3 84:11 86:5 87:5 88:7 91:21 93:15 94:18 97:22 98:7,15 100:17 102:17 105:9,12,21 107:19 110:20 112:20 113:16 114:6 115:2, 12 117:14,18 118:2,10 119:3 120:13 121:20 126:13,13,17, 18,19 127:8 132:18 139:19 141:5,6 143:22 145:10 147: 10 148:8 151:8 152:8,13 154: 2,3 157:21 158:1 162:7 163: 6 169:10,11 174:17,22 175: 10 177:3 178:5,13 179:8,14, 15 183:18 184:10 185:3,7,8,9 191:15 193:15 194:6,7,9,11
---	---	---	--

<p>196:3 197:5,14,15,18 198:14 199:1,20,22 200:8 201:20 202:5,11 205:14,16,22 206:4, 5,6,7,10,19,20 207:2 208:11, 11,14,16,19 209:2,8 210:7,12, 16,17,18 211:2,6,15,16 212:1, 14,22 213:5,6,8,12,22 214:21 217:1 218:9 219:12,13 220:7 221:5,7,8 222:9,18 223:2,10, 11,14 224:5,11 230:20 231:5 232:14 233:4 234:2 242:11 244:22 245:6 247:16,17,21 248:1,3,6,8,13,14 249:16,20 252:11,13 257:5 263:7 265:6 266:10,12 271:12 275:18,18 277:18,19 278:11 279:3,7,14 280:21 282:17,22 286:3 287: 7 289:12 291:10 294:20 296: 4,22 297:5 299:8 300:14 303: 6,10 304:6,18,19 306:7 311:3 315:9,18 318:1,3,14 319:22 322:15 324:9,10 329:1,14 333:22 335:15 336:18 341: 16 344:9 345:19 346:8 350: 21 351:1 354:16 358:4 359: 15 361:3 364:1,15 365:3,5,14 366:15,19 370:1,2 371:4,14 372:5 373:18 376:21 379:12 381:20 382:2,15 383:18 385: 16,17,21 at-risk [1] 79:8 atherosclerosis [1] 117:18 atoigo1@verizon.net [1] 386:2 attached [1] 325:2 attack [1] 139:1 attacking [1] 331:15 attacks [3] 124:17 138:8 226: 18 attain [1] 91:22 attempt [15] 16:20 18:13 19:9, 11 20:11 22:5 23:13,18 24:4 25:13 30:3 31:3 102:19 112: 17 120:6 attempted [1] 17:19 attempting [1] 271:10 attempts [9] 25:15,17,18 120: 8,16 122:5 274:19 285:1,6 attendance [1] 223:10 attention [6] 33:2 92:22 101: 10 217:22 264:8 305:20 attenuate [1] 60:3 attenuated [1] 253:5 attitude [1] 348:6 attributed [4] 101:18 110:18, 22 115:5 attributes [1] 169:18 attrition [7] 173:22 230:9 253: 20 254:5,13 349:21 366:18 atypical [2] 312:12 314:4 AUC:Cmax [1] 270:7 audience [2] 152:4 330:4 audit [1] 25:21 aura [1] 375:11 Austria [1] 233:5 authorities [3] 101:14 146:5 293:15</p>	<p>authors [2] 29:13 30:21 autocrine [1] 188:9 automatic [1] 144:1 automatically [1] 103:4 autonomic [1] 225:6 available [20] 12:18 13:1 127: 7,15 130:8,11 139:21 161:21 162:5 163:8 166:15 219:9 245:3 250:19,20 251:5 335: 13,19 337:15 355:22 average [9] 71:9 174:18 176: 14,14 228:9,12 234:12 258:1 289:6 avoid [2] 29:8 103:5 avoided [1] 367:15 awake [1] 58:22 aware [4] 5:15 9:22 216:7 219:7 awareness [8] 141:11 142:4 151:5,14,14 152:18 153:10 159:10 away [1] 316:4 axis [2] 187:11,11</p> <hr/> <p style="text-align: center;">B</p> <hr/> <p>back [36] 34:6 50:11 70:19 102:9,11 106:7 108:22 130: 10 133:1 149:18 151:5 156: 13 157:2 174:16 177:1 181: 11,21 183:8 222:13 233:4 238:21 241:22 246:20 308:9 318:20 324:17 330:21 336:3 338:15 352:20 353:4 357:10 365:4,5 372:4 377:3 back-of-the-envelope [1] 355:12 background [10] 51:12 87: 13 92:10 99:19,21 100:1 136: 3 290:5 312:15 365:22 backup [1] 176:6 bad [2] 25:1 329:20 balance [11] 128:14 164:2 170:3 186:21 225:15 263:17 268:16 301:14 351:10 367: 22 374:10 balanced [4] 77:19 100:13 300:15 343:18 band [4] 162:10,16,20 163:6 bar [2] 171:14 336:20 Barbehenn [1] 224:4 Bariatric [3] 71:19 74:6 245:3 barrier [1] 220:7 basal [4] 51:20 190:17 225:4 261:3 base [3] 91:17 117:7 239:11 Based [42] 8:19 13:1 16:22 29:18 44:12 45:17 46:5 73:4 75:18 96:3 109:16 110:8 119: 22 120:13 123:2 130:14 139: 11 155:16 156:6 163:11 169: 6 194:19 198:15,20 208:3,6,8 211:2 213:13 236:4 238:6 248:7 250:5,6,7 276:6 297:2 343:10,19 382:22 383:12,14 baseline [31] 54:9,22 63:7 77: 13 78:9 81:9 82:1,21 83:7,11 84:12 85:3 86:7 88:8 145:10 241:22 275:16 279:12,17,22</p>	<p>280:1,7,10 291:10 307:20 308:1 318:2,10,12,17 350:20 bases [1] 144:1 basic [5] 16:12 238:10 302:8 366:3,4 Basically [5] 121:8 217:16 310:8 326:12 345:8 basis [7] 39:8 65:7 70:12 148: 7 232:15 270:9 320:12 battery [2] 204:20,21 be [314] 8:9 10:2,21 12:2,8,17, 21 13:3,15,22 15:16 16:3 18: 19,20 21:12 23:22 24:12,12, 16 25:17 36:14 37:1,8,17 38: 10,22 39:18 40:8,10 41:17 44:6,7,15,16,22 47:3,12,21 49:2 51:13 52:16,21 53:19 54:12,19 55:14 57:9 60:22 63:10 70:11 71:19 73:8,11 79:17 84:19 89:5,21 90:5 92: 12 97:6,11 112:10 113:3 116: 21 117:7 121:4,7,10 125:3,11 126:4 129:18 131:14 133:15, 16 134:19 136:7,14 137:6 138:1,6,17 139:2,21 141:12 142:1,2,6,7,9,12,19 143:8,21 146:7 147:5,11,20 148:1,2,5, 6,10,14 149:7,13,14,15,20 150:14,16,18 151:12 152:2,6, 7,12 153:2,10,15,16 154:14 155:4,6,13,16 156:20,22 157: 4,19 162:9 163:1,12,22 166:4 167:17 170:11 171:21 178: 14 180:13,15 181:6,17 182: 18 184:8 185:7,10 189:7 191: 10 195:4,14 199:12,14 201:6, 7 205:19 206:3 210:12 212: 13 214:16,19 216:14 217:8 222:3 224:4 228:3,17,21 231: 17,21 232:14,15 233:7,22 234:5 235:21 237:1,15 238:1, 1 239:1,19 240:11,13,15 241: 2,17 242:7,8 244:21 245:21 248:9 250:19,20 251:12 252: 7,8 253:7 255:19,22 263:6 264:20 270:12 273:18 274: 20 277:13 278:14 281:13 282:9 283:19 284:3 287:8 288:12 290:22 293:5 297:9, 22 298:1,4 299:9,12 302:16 304:8 305:7 307:8,11 308:18 312:20 315:15 317:13 321: 21 323:1,7,20 326:16 332:7,8, 10 334:16,18,18,20 335:2,4, 14,15 336:20 337:4,6 340:21 343:6,7,12 345:16 347:8 349: 1 350:11,16,21 352:5,7 354: 16,19 356:8,18,19 357:3,17 358:21 361:9 362:5 363:13, 21 364:1,21 365:1,10,11 366: 17 367:7,9,10,15,19 368:18 369:1 370:7,12 371:2 373:2, 3 374:2,18 375:8,15 376:3,9, 22 378:13 379:6,16,17,19,21 380:1,5,7,10 381:5,15,20 383: 2,16 385:4 bear [2] 280:4 301:2</p>	<p>became [2] 118:13 380:3 because [104] 18:10,20 21:12 22:15,17 27:3,8 31:4 48:17 79:14 101:5 104:19 106:10 110:6 116:5 120:1 129:12 134:1 136:3,21 161:4,15,22 167:20 174:1 176:13 181:18 201:3 207:6 212:11 219:17 220:4 226:9 230:2 232:9 234: 18 238:3,5,11 239:19 257:2,8, 22 258:6 264:22 269:3 277:9, 12 279:1,10 281:1,13 285:15 294:6 297:1 300:18 301:6,11 302:21 304:20 306:14,15 308:5,12 309:18 312:13 315: 12 316:4,11,12 319:1 323:15 324:1,5,20,20 325:18 331:5 332:16 333:9,22 334:21 335: 17 346:15 349:2 350:2,3 357: 1 359:1,10,15 360:20 362:15, 18 363:13 364:22 366:18 367:2 378:5,14,19 379:13 380:7 382:8 become [3] 263:11 288:1 378: 6 becomes [2] 66:9 382:12 been [128] 8:22 9:11 14:4,6 17:7,7,8 18:9,11 21:16 22:10, 13,14,16,21 27:11 31:19 35:3 38:2,19 41:14 42:2,13 46:9 48:21 54:14,16 61:7 72:5 87: 16 94:16 17 96:21 110:20 117:19 120:15 122:14 127: 10,18 129:1 133:10 134:9,19 136:5 137:17,19 139:9 141:1 144:20 149:21 150:1,3,5 158: 4 165:18,21 166:20 167:10 168:16 174:22 183:17,22 184:14 185:19 187:5 189:1,5, 7 196:13,16 197:11 198:1,11 207:11 216:8 219:6 227:18, 22 228:14 236:5,8 241:14,16 245:14 258:21 260:17 267: 14 268:3 269:11 271:3,12 272:10 282:7,17 286:13 287: 19 292:16 293:13 294:13 296:14,16,18 306:7,15,16 312:10 314:13,17 319:5,12, 13 320:16,17 339:8 343:5 346:15 349:17 351:15 352: 10 354:5 359:12 362:14 364: 18 365:17 369:4 370:4 373: 22 379:18 Before [29] 5:12 18:5 26:6 41: 20 43:11 57:1 90:19 128:4 129:1 130:22 132:13 144:9 151:19 180:9 184:21 222:7 231:15 240:1 287:4 324:17 325:22 330:20 334:4 336:14 353:16 355:20 358:21 372: 21 383:6 began [3] 17:12 66:3 294:16 begin [5] 11:7 16:9 94:1 159: 14 329:1 beginning [7] 96:8 223:2,11, 15 330:21 372:6 381:10 behalf [4] 9:3 13:12 242:22</p>
--	--	---	--

<p>320:9 behave ^[1] 56:1 behaves ^[1] 58:17 behavior ^[17] 16:19 22:12 24:10,17 29:21 30:15 54:3 108:17 110:1 119:19 121:16 122:3,12 161:18 187:16 194:10 202:11 behavioral ^[3] 73:7 201:15 244:4 behaviors ^[3] 16:12 22:6 261:5 behind ^[2] 12:16 329:6 being ^[39] 10:19 27:20 44:21 73:22 100:18 122:20 126:3 136:22 137:5 143:6,17 149:11 155:19 156:17 162:10 168:1 172:17 178:15 236:9 238:12 239:8 242:1 255:13 257:3 266:9 296:7 305:8 320:18 326:12 332:9 350:10 356:22 358:7,7 362:17 365:9,11 380:5,6 belief ^[1] 255:21 believe ^[28] 12:18 13:2 163:13 170:2 218:20 222:16 233:5 236:4 274:10 287:14 289:22 290:21 291:22 292:7 295:7 318:15 325:4,19 335:8,18 337:14 342:14 348:11,21 349:12 351:18 382:14 383:15 believed ^[1] 274:2 believes ^[2] 222:20 243:22 below ^[12] 57:5 114:7 182:14 208:11,13 211:1,6 212:22 228:12 291:15 325:11 363:12 Ben ^[1] 224:6 beneficial ^[8] 60:10 68:11,19 72:13 170:20 172:8 201:4 203:11 benefit ^[34] 31:14 37:16,22 40:15 89:6 148:1 154:9,10,19 157:8 158:15 159:6 161:4,18 162:8 165:7 224:10,17 238:6 343:15 344:12,16 346:11,16 354:17 357:10 359:4,20 360:9 361:15 362:5 364:4,7 374:9 benefit-risk ^[2] 134:16 155:19 Benefit/Risk ^[4] 3:23 158:11 234:15,19 benefits ^[19] 32:17 74:9 81:18 91:14 138:7,18 159:2 164:18 165:2,17 166:15 170:4 244:22 297:8 298:12 334:5 357:18,18 363:9 benign ^[3] 230:3 303:14 305:8 benzodiazepine ^[1] 197:12 besides ^[1] 289:5 best ^[6] 26:22 164:21 230:20 315:2 375:5 378:1 beta ^[3] 60:2,3 166:9 beta-blocker ^[1] 281:14</p>	<p>beta1 ^[1] 60:4 better ^[30] 22:18 29:8 30:6,7,13 32:17,20 35:5,17 75:12 90:13,17 97:7 101:20 121:3 155:8 170:5 230:2 294:9 302:8 316:15 332:16 334:2 350:3,3 375:4 376:13 382:1,1,5 between ^[53] 11:11 17:1 29:11 32:12 39:22 50:19 55:17 61:19 69:15 79:11 89:2,11 98:22 99:4 104:8 107:16 114:15 122:15 125:16 137:19 148:3 154:17 160:1,6 164:5,6 170:3 171:13 190:12 191:18 214:3 229:6,19 259:16 261:11 272:13 278:18 279:2 287:8,15,20 289:18 305:12 311:12 317:17 325:8 344:14 353:9 354:12 358:6 367:11 368:16 374:7 beyond ^[3] 64:3 348:20 382:20 bias ^[13] 21:14 27:15 30:6 254:15 287:17,17 289:21 290:13,22 359:7 361:9 372:16,16 biased ^[1] 163:20 big ^[14] 11:12 130:5 237:16 239:22 240:11 315:10,11 325:14 352:9 371:6,19 372:6 376:4 380:17 bigger ^[1] 325:17 bilateral ^[2] 127:12 305:6 billion ^[1] 71:15 bind ^[1] 188:20 binding ^[8] 52:22 54:4 55:14 56:12 197:6,18 198:4 203:1 binds ^[2] 193:6 197:5 biologic ^[1] 366:4 biological ^[3] 65:7 362:9 366:3 biologically ^[4] 268:22 274:9 292:8 361:6 biology ^[2] 366:2 370:14 birds ^[1] 202:20 Birmingham ^[1] 7:6 birth ^[1] 231:7 bisphosphanate ^[1] 166:7 bit ^[16] 33:22 35:3 58:17 61:6 86:12 144:6 175:14 176:17 219:17 300:15 314:18 345:16 352:6 353:21 366:11 378:15 biting ^[2] 320:13,13 black ^[1] 55:7 blacks ^[1] 255:19 blame ^[1] 245:16 blinded ^[10] 21:3,6,9,15 97:16 109:4 119:17 120:14 283:13 320:5 blinding ^[1] 230:8 blindly ^[2] 130:7 133:11 block ^[2] 164:12 371:1 blockade ^[9] 52:3 60:11,14,15 158:21 164:8 199:10 214:15,17 blockage ^[1] 211:8</p>	<p>blocked ^[1] 59:2 blocker ^[3] 164:11 166:9 225:20 blockers ^[3] 60:2,3 164:15 blocking ^[2] 52:17 60:7 blogs ^[2] 237:3 353:2 blood ^[12] 58:22 59:2 162:3 164:11,20 234:3 241:11,13,20 242:4 253:15 298:22 blood-brain ^[1] 220:7 blood-pressure ^[1] 360:22 blue ^[2] 22:1 291:11 blurred ^[1] 266:11 BMI ^[33] 38:14 47:4,6 62:2 70:6,7 73:4,8,9,11 74:11,11 77:22 78:2 86:10 117:6 162:11,17 176:18,20,21 241:10 242:9,12 287:12 307:20 308:1,6,7 310:14,15 363:13 383:17 BMIs ^[3] 355:9,15 363:12 BMR ^[1] 326:9 boats ^[1] 107:1 Bob ^[5] 7:6 218:12 352:17 380:15 383:4 bodily ^[1] 179:1 body ^[53] 13:5 63:17 64:3 67:5 68:8 69:16 71:9,10 72:6,9 75:13 80:9,11,17 85:2,3,11 86:9 89:3,12 92:9,13 103:6 168:13 171:20 172:1 174:15 176:5,7,8,11,15,19,20,22 177:2,8,9,15 200:11 201:3,8 202:8 213:6 224:12,21 244:21 252:14,22 297:5 305:5 333:2,8 bone ^[1] 59:20 book ^[1] 93:22 boss ^[1] 350:10 Boston ^[1] 7:9 both ^[66] 18:17 29:21 32:17 38:3,14 42:22 45:15 48:9 52:1,18 61:9 62:3,5 64:20 67:6,14 77:1 82:3 87:18,20 88:1 99:20 101:2 105:17 107:3 133:8 143:22 144:1 146:22 151:20 152:10 157:14 159:17 176:3 178:8 186:17 190:18 191:4 192:15 193:15 200:2 202:4 203:22 204:22 209:17 219:19 222:16 227:5 230:1 232:6 252:17 255:11 261:7 267:22 284:15 289:14 298:9 301:5 327:21 330:22 338:18,21 350:1 352:16 373:17 385:16 bothered ^[2] 150:1,5 bottom ^[1] 201:2 bound ^[2] 42:18 325:10 box ^[1] 265:12 boxes ^[2] 22:1 30:12 boyfriend ^[1] 24:19 BRADLEY ^[4] 303:5,5 304:18 320:8 bradycardia ^[1] 233:21 brain ^[22] 51:20,22 189:12 190:13 191:7,15,17 198:22 216:22 218:5 220:11,13,17,</p>	<p>17 224:20 225:2 226:6 237:18 261:4 270:6 273:17,18 branches ^[1] 234:11 break ^[9] 11:21 61:19 180:9 184:11 185:7 283:6 325:22 327:2 328:15 breakdown ^[1] 275:15 breakfast ^[1] 42:9 breaks ^[2] 103:12 351:11 breast-cancer ^[1] 365:11 brief ^[13] 5:20 10:10 37:12 185:1 186:4 216:11 246:20 276:19 303:3 304:16 320:2 367:3 370:12 briefing ^[9] 41:9 82:6 93:22 177:5 230:12 308:13 310:7,11 349:3 briefly ^[17] 42:11 43:9 49:21 117:16 128:9 137:9,10 152:9 186:9 192:2 225:1 251:16 286:19 299:3 322:2 323:14 367:16 bring ^[2] 327:1 380:19 bringing ^[4] 54:8 141:20 242:11 353:8 broad ^[3] 188:14 226:7 307:1 broaden ^[1] 20:19 broadened ^[1] 25:8 brought ^[2] 184:8 240:1 Bud ^[1] 181:11 bulleted ^[1] 274:20 bunch ^[1] 336:13 burden ^[1] 29:19 Burman ^[9] 2:5 8:4,4 317:10,11 367:19 369:8 384:19,20 burn ^[1] 326:6 burned ^[1] 326:8 business ^[1] 222:2 busy ^[1] 126:12 But ^[233] 20:17 21:11 22:7,10,21 23:11 25:12 26:9 28:15 32:15 36:11 38:7 47:1 53:12 56:5 58:20 59:9 62:2,21 63:2 64:4 65:12 71:4 74:7 77:8,18 81:7 82:15 86:11 90:4 95:17 97:11,17 98:11 101:22 103:15 104:21 107:15 118:15 119:7 120:5 122:3 124:20 125:22 126:4,12 127:11,14 128:12 130:1 132:13,18 135:13 141:6 142:4 143:9 147:3 149:3,13 153:1 157:8 161:5,19 165:2 168:16 174:9 175:21 176:22 178:5,9,16 179:3,5 180:15 182:8,19 183:9 184:2 188:18 189:2 191:5 192:17 199:13 200:15 201:7 205:22 206:3 209:13 210:11,14 211:22 213:22 214:17 216:8 218:9,13 219:4 220:8 224:20 227:15 229:17 234:10 237:14 240:4,11 241:3,7,17 247:10 248:3 253:18 254:5 255:1,9 257:11 258:16 260:18 262:16,17 263:15,19 264:7 265:15,18 269:21 271:11 274:7,22 280:2 285:19 287:11,14,</p>
---	--	--	---

<p>19 288:6,22 289:12 290:8 291:20 292:3 294:4,11,14 298:4 302:18 303:10,16 304: 15 307:11 308:9,11,18,22 312:19 313:16 316:13 317: 18 318:14,16 319:7 321:2,15 322:16 324:10,20 325:4,8,12 326:4,19 327:18 330:19 331: 9,15 332:11 333:4,16 335:7, 14 337:8 339:15 341:5 342: 10 343:2 347:8,21 349:11 350:4,21 351:4,11 352:7,12, 20 355:17 359:19 360:10 362:5,8,21 363:10 364:4,20 365:2 366:11,14 368:7,20,22 369:10,13 370:9,12,15,18,20 371:9,11 372:20 373:3,22 374:5 375:8 376:8,13,14 378: 11 379:11,12 380:13 381:3, 17 382:21 383:5 buy ^[1] 382:22 by ^[207] 5:9,20 8:20 9:8,11,13 11:17 12:1 13:6 15:11,17 16: 11 19:16 21:16 22:4 23:12, 18 24:6 27:22 29:17 37:8,13, 13,14,17,18,19,21,22 39:3 50: 13,14 51:3 54:12 56:12 58:6 59:3,8,10 60:4,6 62:15 63:14 64:5 66:10 67:7 68:9 70:18 71:7 72:21 76:13 78:20 83: 17,20 85:18,18 86:18 87:3 88:5,7,8,15 89:8,18 90:6 91: 2,21 92:13 94:7 97:20 98:7,8, 10 100:18 101:19 107:8 109: 6,14,16 112:17 121:5,18 123: 4 125:10 126:8 127:16 129: 21,22 130:7 131:9,12 132:3 133:12 134:1 135:10 136:10, 22 137:9 138:18 146:8,8 147: 21 150:1 159:5,15 160:22 169:9 171:22 175:1 179:9,10 180:6,14,22 185:10,11,15 186:4 189:22 195:15 196:13 199:15 202:21 204:10,19 207:16 208:13 212:6 214:18 217:15 222:6 225:19 226:8, 12 227:3 228:11 229:17 234: 9 237:1 243:2,19 246:10 248: 14 249:13 250:4 252:11,22 253:8 255:11,15 258:7,16 259:7,20 262:7,13,16 263:3, 14 264:6 265:12 266:21 267: 7,9 269:6 275:15 278:12 279: 7 282:15 283:12 284:2 285: 17 291:11,14 296:7 300:20 303:8 304:9,13 306:7,11 307: 17,20 309:13 319:21 320:1 324:3 328:9 336:17 337:10 338:6 342:2,6,9 344:6 347:9, 13 349:5 357:20 358:19 359: 22 365:21 368:19 370:21 371:7 382:8 383:18</p> <p style="text-align: center;">C</p> <p>C ^[4] 3:1 4:1 5:1 222:1 C-CASA ^[10] 25:4,21 29:6 45: 22 112:17 116:20 119:15 120:14 372:2 373:8</p>	<p>C-CASE ^[1] 109:6 calcium ^[5] 192:20,21,21 193: 12 195:1 calculated ^[1] 345:9 calculation ^[2] 248:20 355: 12 calculations ^[1] 343:9 Call ^[9] 3:2 5:2 18:9 22:19 24: 6,11 30:2,3 141:13 called ^[23] 16:19 17:7 18:2,4, 6,7,12 19:13 20:1 25:15,16, 17,21 27:14 41:8 45:18 91:6 145:2 299:5 304:6 314:18,19 334:8 calling ^[4] 18:18,19 109:8 141:19 calls ^[1] 242:16 caloric ^[2] 65:22 75:6 calories ^[7] 63:20 65:22 326: 5,6,6,7,8 came ^[7] 17:16 20:12 40:4 52: 7 310:3 325:6 367:14 campaign ^[1] 141:11 can ^[162] 18:14 19:6 20:9 22: 12 23:4 24:11,12 27:21 30:4, 9,13 31:21 32:5,14 36:3 39: 19 41:4 51:12 52:21 53:9 54: 6 55:5,14 56:22 58:6 62:22 63:15 64:16 65:12 70:11 72: 16 73:20 75:15 80:14 99:11 100:14 103:21 106:12 107:9 108:9,10 112:10 131:18 138: 6,16 143:5,5 160:17 161:9 164:12 170:3 171:21 172:12 174:5,5 175:10,12 177:1,6,12 182:20 185:13 192:14 193: 14,18 194:5,12,14,22 195:13, 14,16 196:9 197:16,18 198:2, 14 200:14 201:4 205:15 206: 7 209:19 236:7,20 237:16 238:18 245:20 248:11 250: 15 254:15 256:6,18 262:12, 17 263:13 264:5,17 265:11, 12,17 267:4 271:18 272:2 279:5 285:17 286:4,6 292:2 294:7 295:16 299:22 301:14, 17,17,18,18 302:16 303:20, 21 304:15 307:8 309:19 310: 20 311:5 313:17 314:21 315: 3,22 317:13 321:22 329:9,18 333:18 334:20 335:7,8 336: 11 339:5,11,19 340:5 342:11 345:18 346:21 349:21 350:1 360:17 370:7,8,11,20 373:6, 10 374:19 375:5,7 376:12 377:16 381:12,20 382:17 385:12 can't ^[9] 161:8 238:4 242:17 304:14 315:11 328:14 348:5 371:22 378:11 candidate ^[1] 355:8 cannabidiol ^[1] 59:14 cannabinoid ^[19] 11:1 50:9 51:6 52:2,8,9 57:11 58:7,15 188:21 189:1 197:11 224:21 225:19 231:16 232:11 273: 22 274:8 312:22</p>	<p>cannabinoid-system ^[1] 233:11 cannabinoids ^[5] 52:18 58:3 59:3 267:3 269:10 cannabis ^[2] 50:13 189:22 cannot ^[4] 54:12 92:12 143:9 172:4 capsules ^[1] 18:1 capture ^[3] 143:5 172:4 260: 20 captured ^[1] 172:7 car ^[1] 351:12 carbohydrate ^[3] 331:19 332: 1,13 carcinogenicity ^[3] 204:17 217:13 231:13 cardiologist ^[1] 149:13 cardiologists ^[1] 159:5 Cardiology ^[1] 144:3 cardiovascular ^[25] 41:7 47: 5 70:21 72:7 78:9 98:1 100: 17 118:6 138:19 139:2 159:5 187:9 218:15 219:1 224:18 225:10 226:4 233:20 298:14, 19 299:7,9,12 328:11 348:19 care ^[16] 60:22 141:6,9 142: 10 143:22 145:1 149:12 152: 1 159:9 166:12 168:4,20 245: 11,18 334:6 339:9 care's ^[1] 146:5 carefully ^[10] 226:9 235:4 298:6 313:3,3 330:19 334:3 341:7 371:3 380:6 caregiver ^[1] 154:18 Caroline ^[5] 4:10 243:7,9,11 246:15 Carpenter ^[13] 2:6 8:2,2 14:3 217:21,21 314:7,8 365:20,20 379:17 384:17,18 carried ^[4] 172:19 173:16 254:22 359:8 carries ^[1] 71:20 carry ^[1] 241:1 carryovers ^[1] 358:20 case ^[53] 19:8 22:19 27:22 80: 9 83:6 100:15 103:18 104:3 105:17 112:8,17 116:20 117: 11 118:21 119:1 120:3,5 125: 2,10 126:12 127:3,5,8,11,18, 21 128:12,19,20 129:3 161: 17 224:17,19 231:16 247:22 249:2,17 266:3 267:19 268:2, 5 282:12 287:3,11 293:3 319: 6 327:19 341:2 360:13 362: 18 364:7 371:10 376:6 case-report ^[6] 258:20 266: 15,19 281:16 282:15 303:11 cases ^[95] 25:15,16 26:8 100: 2 102:5,12,16 110:11,14,18 111:6 113:6,8 117:9 119:18 120:8 123:17 124:16 125:5,6 126:9,10,18,20 127:10 128:8, 10 129:12,21 130:1,7,16,20, 22 131:12,18 132:1,2,4,5,14, 15 133:2,3,10,14 136:14 137: 16 259:1 267:12,14,17 268:1 269:8 270:22 271:3,6,9,11,16,</p>	<p>22 272:1,10,11,18 282:16,19 283:14,15,17,19,20 284:21 285:2,5,9 286:15,19 294:3 295:2,4,15 296:12,15,17,20 304:20 305:12 320:6 331:10 341:11,19,20 342:5,5 categories ^[8] 111:5 124:3 283:5,6,7,8 308:6 310:14 category ^[8] 107:13 124:18 161:2 167:5 262:12 263:13 264:5 283:18 Cathy ^[4] 2:3 3:6 7:2 8:12 caucasian ^[3] 63:1 255:7 323:6 Caucasians ^[2] 255:18 368: 10 causal ^[6] 27:13 122:14 136: 5 182:17 292:6,7 causality ^[1] 27:8 cause ^[14] 159:17 195:20 200: 9 209:4 217:17 232:19 233: 16 237:9 249:22 291:17 337: 3 341:14 360:17 378:20 caused ^[6] 224:18 226:8,9,12 227:3 331:12 causes ^[11] 60:20 212:7,9 216:16 233:10 244:3 249:18 304:4 331:16 378:22 379:4 causing ^[2] 27:10 212:20 caution ^[2] 358:8 362:18 cautious ^[2] 380:1,10 caveats ^[1] 253:18 CB ^[4] 195:9 196:9 201:6 225: 12 CB1 ^[77] 42:4 50:16 51:16,19 52:12,17 53:1,11 56:7,12,19 57:8,17 59:9 60:7,11,14,15 68:4,15 158:21 164:7,8,15 188:22 189:10,11,17,22 190: 7,11,12,19 191:3,6,14,14 192: 4,14 193:6,7 195:6,8 196:2, 15,21 197:17 198:3,7,12 199: 22 200:21 201:10 202:18 203:16,21,22 204:2 207:11 211:8,11,19 213:16 214:11 219:18,19,20 224:21 226:7 233:5,17,20 267:6 269:17 273:16 292:9 326:19 CB1's ^[1] 219:22 CB1-deficient ^[1] 233:13 CB1-receptor ^[1] 261:1 CB2 ^[8] 50:16 53:2 59:13 188: 22 189:4,9 219:18,19 CD2 ^[1] 267:6 CDC ^[1] 33:8 CDER ^[1] 370:4 cell ^[2] 56:5 193:5 cells ^[6] 64:21 194:1,2 226:5 231:12,13 cells' ^[1] 193:11 cellular ^[3] 188:11 194:7,11 CENTER ^[6] 1:3 6:18 7:1 8:5 75:1 321:1 Centers ^[1] 7:21 central ^[37] 61:8 67:6,14 86: 19 185:21 186:8,11,17 189:6, 12 190:11 195:6 198:18 199:</p>
---	---	---	---

11,13,18 202:21 203:20 205:2,4 206:7,15 207:8 211:21 212:10,12,18 213:1,7,11,14, 20 214:8 215:9 261:7 292:10 304:6 central-nervous-system-a-cting ^[1] 372:7 centralized ^[2] 43:14,21 centrally ^[5] 101:2 219:20 220:1,5 296:1 cerebellar ^[3] 56:9 225:5 304:3 cerebellum ^[2] 190:17 261:2 cerebral ^[3] 58:22 59:2 191:1 certain ^[5] 51:13 225:22 228:18 304:5 359:9 certainly ^[9] 32:11 110:13 226:1 240:3 299:1 324:3 347:19 348:4 360:1 cessation ^[8] 40:10 94:14 114:17 322:6,8,20 346:19 363:19 cetera ^[17] 19:4 20:11 27:18 28:10 31:7 35:12 36:4 149:14 154:22 171:17,18 218:6,6 305:20,20 353:3 378:16 CFR ^[2] 141:16 150:15 Chair ^[4] 5:6 10:17 49:5 374:4 Chairman ^[16] 6:17 7:8,16 36:18 49:3,14 69:9 93:9 139:5 140:1 158:12 170:7 181:12 251:9 329:15 370:11 challenge ^[1] 34:7 challenged ^[1] 16:11 challenges ^[1] 192:12 challenging ^[1] 139:3 chance ^[4] 292:2,3,3 333:14 change ^[16] 25:1 56:12 57:13 61:5 72:19 86:19 128:3 238:17 242:4 255:17 291:10,12 308:17 338:14 367:4 374:9 changed ^[1] 286:7 changes ^[18] 60:16 86:20 124:1,9 146:21 151:16 154:20 178:20,21 238:16 260:16 262:4,9,9 358:5 373:17,19 382:15 changing ^[2] 236:11 340:2 channel ^[2] 193:12 194:22 channels ^[9] 53:6,8 59:14,15 192:20 195:1,2,4 218:18 characteristics ^[3] 82:22 123:7 348:10 characterization ^[4] 42:6 266:2 375:4 382:5 characterize ^[1] 12:19 characterized ^[2] 165:18 260:18 characterizes ^[2] 335:20 337:15 chart ^[3] 53:12 160:7,8 charting ^[1] 154:19 check ^[1] 141:14 checked ^[1] 371:9 checklist ^[3] 148:21 152:19 237:14	chemically ^[1] 183:10 chest ^[1] 123:19 Chew ^[13] 3:20 37:19 40:10 93:3,6,8,13 140:2 179:10 180:17,17 181:2,21 chief ^[2] 324:12 330:5 Child ^[2] 9:14 14:22 child-bearing ^[3] 323:8,9 352:18 childhood ^[1] 319:20 children ^[4] 184:3 319:16,19 321:3 chill ^[1] 238:20 choice ^[1] 161:19 choices ^[1] 73:17 cholesterol ^[13] 67:17 78:13 83:20,22 90:9 92:6 164:20 241:11 253:9,13,14 297:7 298:22 choose ^[2] 223:13 241:8 chose ^[1] 316:3 chosen ^[1] 156:6 chromosome ^[1] 231:11 chronic ^[20] 47:8 60:14,20 65:16 68:6,12 73:13 85:8 146:18 158:17 204:14 209:6,11, 14 217:9 244:6 245:22 257:3 364:22,22 chronically ^[1] 61:3 chronicity ^[1] 373:16 chronotropic ^[1] 60:3 cigarette ^[1] 256:8 Ciraulo ^[13] 2:12 7:8,8 35:6, 19 219:3,3 312:7 349:16 351:20 377:13,13 384:5 circles ^[2] 291:12,19 circulated ^[1] 287:8 circulating ^[2] 61:15,21 circumference ^[1] 78:4 circumstances ^[4] 24:12 307:5 333:5 335:5 cirrhosis ^[1] 52:14 CIRUALO ^[1] 349:16 Citizen ^[1] 224:2 Citizen's ^[1] 4:4 citizens ^[1] 70:4 claim ^[3] 348:12 349:8 382:19 claiming ^[1] 348:19 claims ^[3] 144:1 236:5 382:14 clarification ^[12] 15:11 222:8 246:17 250:12 271:16 305:15 310:3,21 320:3 327:9 345:4 384:22 clarified ^[1] 239:19 clarify ^[10] 15:14 35:8 178:17 182:6 219:16 249:4 273:3 287:5 302:8 310:20 Clarifying ^[4] 3:25,29 170:14 215:15 clarity ^[2] 16:11 112:3 class ^[14] 10:22 166:19,22 190:7 212:6 213:21 214:11 231:21 232:10 276:9 302:15 310:15 336:12 385:10 classes ^[2] 162:4 167:1 classic ^[3] 54:3 56:22 375:18	classical ^[1] 50:20 classically ^[1] 377:9 Classification ^[13] 11:9 15:20 16:1 20:1 21:4 103:8 110:9 112:18 116:22 119:21 123:4 181:6 283:6 classifications ^[1] 22:9 classified ^[4] 17:9 112:8 304:22 305:3 classifying ^[1] 20:6 clear ^[16] 161:4 172:11 217:8 233:19 238:15 239:9 240:21 319:1 326:14 351:1 357:15 359:4,19 361:4 364:16 371:2 clearly ^[22] 24:17 32:11 38:13 57:5 64:22 66:21 145:17 147:21 148:14 157:12 159:11 167:15 177:16 180:18 198:17 207:8 209:19 210:14 220:19 234:17 295:6 296:6 Cliff ^[1] 10:13 Clifford ^[4] 2:2 3:3 5:5 7:4 clinic ^[2] 215:11 371:8 Clinical ^[101] 3:16,19 4:14 15:4 16:14,18 17:16 31:15 32:3 34:21 37:4,16,22 40:5 49:17 54:11 65:7 69:3,5,7 74:14 75:19 92:18 93:4,7,13,14 97:15, 21 100:16 101:8 103:16 109:5,10 112:6 116:19 117:8,10 119:17 121:2 126:11 132:9 134:8,10 136:2,9 138:5 157:20 159:2,6 165:18 166:6 174:8 186:10 200:12 203:4 204:8 205:5,8,8,18 206:1,16 208:8 210:1 211:2,17 212:14,17 213:5,13 214:7 215:4,6 222:5 226:1 229:15 235:1 246:4 247:18 248:4,6,15 249:2 250:1 251:8 252:5 260:18 267:2 271:4 273:2 276:5 286:16 289:16 292:14 293:19 299:4 322:3 346:16 371:5 377:16 clinical-study ^[1] 258:19 clinical-trial ^[2] 269:6 286:14 clinically ^[9] 57:8,10 68:3 170:1 199:20 214:21 270:14 274:15 299:15 clinician ^[1] 246:1 clinicians ^[2] 165:12 245:17 clinics ^[1] 32:7 clonic ^[1] 210:10 cloning ^[1] 50:15 close ^[6] 80:17 124:20 205:17 212:9 231:5 327:2 closely ^[5] 53:3 70:5 120:18 151:1 157:13 closer ^[2] 309:21 381:4 clumsiness ^[1] 263:18 Cmax ^[2] 208:7 248:7 CNA ^[1] 195:9 CNS ^[12] 64:5,22 205:12 206:6 212:3 214:18,21 249:2,18, 22 366:5,15 co-investigators ^[1] 16:1 co-morbidities ^[2] 78:6 154:13	co-morbidity ^[1] 79:7 coach ^[1] 380:21 Cochrane ^[1] 234:9 code ^[1] 154:12 coded ^[2] 129:22 373:4 codes ^[2] 23:3,5 Coffin ^[10] 2:11 7:10,10 323:3, 3 352:1,1 354:1 378:10 384:6 cognition ^[1] 194:10 cognitive ^[10] 124:2 125:7 187:16 191:2 260:16 262:4 264:2,2,9 305:18 cognitively ^[1] 307:11 Colesville ^[1] 1:10 collaboration ^[4] 14:11 29:11 144:4 234:10 collaboratively ^[1] 224:3 colleague ^[1] 179:10 colleague's ^[1] 381:7 colleagues ^[4] 109:14 121:6 135:21 376:6 collect ^[3] 31:5 41:16 156:9 collected ^[4] 28:9 94:22 98:6 111:8 collection ^[4] 102:20 109:13 362:12,13 College ^[2] 144:3 157:22 Colman ^[17] 2:23 3:8 6:10,10 10:10,13 37:8 182:3,4 184:9 221:3 293:20 294:2 314:15 338:4 339:14 376:5 Columbia ^[14] 11:8 15:5,19 19:16 20:1 23:14,15 29:5,12 283:1,5,8,18 378:3 column ^[3] 201:16,19 295:11 combination ^[3] 46:18 78:13 338:20 combinations ^[1] 162:5 combined ^[5] 168:2 230:5 264:17 265:11 357:6 come ^[17] 25:5 151:5 157:2 172:13 222:12 246:20 293:21 312:1 327:7 328:4 330:21 335:8,11 336:3 365:4 369:4 377:3 comes ^[7] 23:13 62:11 64:8 182:10 330:16 345:11 365:5 coming ^[4] 14:15 45:18 80:8 320:22 comment ^[20] 10:7 53:14 178:11 198:16 216:9 234:21 235:17 250:15 258:16 304:16 323:13,14 324:12 329:16 338:2 347:13 367:6 369:11 372:12 374:13 comments ^[24] 10:15 36:7 175:3 219:15 220:21 246:2 250:10 310:1 313:3,11 329:18 365:21 367:20 369:12,19 373:9,9,12 377:11 381:8 383:5 385:7,10,19 commercial ^[1] 143:15 commissioned ^[2] 15:16 19:16 commit ^[1] 33:11 commitment ^[3] 10:19 240:
--	---	---	--

<p>21 241:1 committed [6] 23:19 91:16 118:15 151:6 157:12 287:4 Committee [58] 3:25,29 4:16 5:5,6,22 9:5 10:18 12:9 13: 13,22 14:4,6 33:17 36:19 37: 6 46:12 48:11 49:15 69:9 93: 10,22 100:19 121:1 138:10 139:6,22 140:4 158:13 170: 12,14 184:15,18,20 215:15, 16 217:20 220:22 222:12,20 223:4,12 249:6 250:11 251:2, 10,20 317:9 327:3 328:16 336:18 352:3 367:8 369:21 372:10 385:5,6,17 committee's [1] 246:22 committees [1] 14:9 common [15] 19:17 24:5 35: 21 58:2 98:14,19 99:3 126:3 166:3 173:21 260:5,17 288: 11,22 320:21 commonly [2] 153:14 297:20 communication [2] 14:11 288:5 community [2] 32:7 246:5 comorbid [2] 13:7 383:19 comorbidities [16] 38:15,16 43:18 47:7 70:17 71:1 72:11 73:5 74:11 76:8 147:2 164: 14 165:6 241:11 244:12 332: 18 comorbidity [2] 73:9 330:6 companies [6] 15:18 18:18 20:8 21:2 25:16 243:16 companion [1] 95:17 company [24] 9:7 21:8,9 26:6 37:2 229:17 232:2,16 237:12 239:14 240:17,20 241:2 267: 16 280:9 320:9 328:1 338:5, 6,8 344:19,19 367:11 374:2 company's [1] 361:3 comparable [5] 123:8,14 136:2 346:13 382:18 comparative [1] 182:21 compare [6] 26:7 132:11 162: 4 327:17 339:5 382:16 compared [37] 26:15 53:10 61:18 70:7 75:11 82:5,17 84: 12 88:18 90:14,17 91:11 98: 22 104:22 111:18 123:11 124:10 126:2 131:5 135:14, 14 166:19 169:13 174:21 176:16,19,21 177:9 191:7 208:7 210:11 227:20 228:16 247:18,21 288:13 294:12 compares [1] 295:19 comparing [1] 347:7 comparison [9] 131:1 133:5 162:9,13 163:13 166:18 178: 22 259:12 380:8 compassion [1] 245:19 compel [1] 143:9 compelling [1] 28:18 compensated [1] 303:8 compensation [1] 15:21 compete [1] 198:2 competing [2] 9:9 243:15</p>	<p>competition [1] 207:19 competitors [2] 9:17 223:6 complains [1] 301:13 complementary [4] 124:4 266:16,19 306:20 complete [11] 11:17 45:12 46: 10 96:1 143:9 183:16 232:17 254:14 258:20 309:6 339:17 completed [43] 22:4 31:8 39: 14 40:19 45:15 46:10 94:4 95:14 102:3 109:5,8 112:15, 16,19 116:19 117:4,8 120:15 121:13,20 122:3 129:20 131: 3 132:9 133:21 136:2 145:11 163:2,2 180:19 230:18 254: 17 258:19 260:21 271:4 286: 13 299:13 300:10 309:10,16 310:22 312:3 328:6 completely [1] 335:9 completer [3] 79:9 80:18 83: 11 completers [3] 80:11 81:9 83:7 completing [3] 309:7 311:20 379:21 completion [4] 175:11,14 310:22 311:14 complex [14] 57:12 58:17 60: 1 186:15 193:10 194:5 195:5 199:8 200:17 204:3 214:14 244:3 319:18 320:16 complexes [2] 195:10,11 complexity [2] 195:14 257:9 compliance [1] 175:18 complications [9] 71:21 74: 7 159:21 160:20 162:12 163: 5,15 169:17 265:1 comply [1] 91:15 component [2] 59:17 246:19 components [2] 187:20 188: 17 composite [4] 264:14 278:5 285:18 318:5 composition [2] 238:16 300: 11 compounds [3] 296:13 314: 13,16 comprehensive [8] 129:19 146:19 157:22 168:3 230:15 262:17 263:19 299:6 comprise [1] 51:7 comprised [3] 76:1 96:16 187:19 concealment [1] 230:8 concede [1] 316:6 conceivably [1] 234:5 concentrated [2] 291:19,20 concentration [5] 55:9 198: 20 220:11 249:13,14 concentrations [12] 54:7 55: 2 56:11,15,21 57:3,9 64:16 68:3 190:19 199:3 250:3 concept [3] 54:13 192:12 287:19 conceptually [1] 149:3 concern [34] 11:12 12:12 69: 19 108:15 138:4 165:11 205:</p>	<p>3 227:17 229:4 232:19 233: 16 246:21 255:5 257:3 258: 13 264:22 266:1 287:18 298: 10,17 321:7 329:3 336:7,10 340:8 341:20 357:9 361:2 362:1 364:14 365:15 366:9, 16 374:5 concerned [22] 70:22 218:22 272:22 310:16 312:13,17 313:16 323:7 336:10 340:10, 18,18 342:11,16 343:3 347:2 352:15 362:6 366:11 368:4,9, 12 concerning [1] 310:3 concerns [11] 12:3 49:18 249:8 251:19 262:3 270:9 306:8 314:3 337:3,7 344:22 conclude [3] 134:14 158:13 186:9 concluded [2] 234:12 319:7 concludes [1] 170:7 concluding [1] 90:19 conclusion [8] 5:19 32:9 168: 7 214:10 281:20 335:11 349: 5 369:5 conclusions [4] 203:3 215:1 230:9 368:2 concomitant [3] 81:3 113:8 323:18 concordant [1] 227:15 concurrence [1] 126:5 concurrent [2] 113:12 229:9 condition [8] 13:7 70:11 151: 17 236:22 239:5 244:6 265:3 383:19 conditions [6] 52:13 87:19 244:11 245:22 246:11 273: 14 conduct [1] 94:21 conducted [16] 38:9 39:2,6,8, 9,11 76:2,7,11 85:20 94:12 95:16 116:10 260:10 265:8 322:7 conducting [3] 34:10 254:20 299:5 confer [1] 244:22 conference [2] 81:16 95:2 confidence [14] 26:15 116: 14 131:21 272:6 315:10,15, 21 316:1,18 317:3,6 324:6 325:10,18 confined [1] 277:12 confirm [1] 28:13 confirmed [8] 87:3 88:5 116: 22 127:5,9 128:10 267:14,17 confirming [1] 26:11 confirms [1] 139:8 Conflict [6] 3:5 8:12,14,16,21 320:8 conflicts [3] 224:7 303:7 327: 8 conform [1] 320:20 confounding [1] 103:5 confusing [2] 28:18 302:21 confusion [6] 219:17 247:5,5 248:11,16 249:10 confusional [1] 264:9</p>	<p>congestion [1] 183:5 conjunction [3] 73:15 75:4 270:5 connection [3] 8:22 223:9 330:7 cons [1] 367:22 consequence [1] 379:5 consequences [8] 147:6 168:12 229:14 236:15 238: 11 351:6 361:17 379:3 Consequently [2] 122:14 215:5 conservation [1] 202:20 conservative [3] 21:7 258:8 316:9 conserved [3] 202:18 204:1 366:1 consider [17] 37:7 53:20 71: 11 80:15 90:8 112:1,4,11 126:18,22 236:18 256:9 320: 20 343:6 356:9 363:14 365:3 considerable [3] 254:15 261: 16 366:16 consideration [3] 52:20 244: 2 357:10 considerations [1] 363:8 considered [13] 19:11 73:11 110:4 112:8 172:21 181:4 193:7 252:7 263:5 271:6 283: 19 320:11,17 considering [4] 107:22 111: 9 137:10 357:5 considers [1] 172:18 consist [1] 151:22 consistency [3] 81:13 83:14 112:3 consistent [15] 26:18 32:14 76:15 84:2 92:18 107:15 114: 14 121:21 128:15 134:21 135:13,20 138:12 199:18 215:10 consistently [3] 19:20 63:10 255:18 consequences [1] 351:15 constant [1] 145:20 constellation [1] 297:16 constituent [2] 50:12 188:5 constitute [1] 341:16 constitutive [8] 54:21 192:9 196:20 198:7 201:16,22 202: 11 207:17 constraints [1] 207:6 constructed [1] 21:2 consult [1] 376:6 Consultants [5] 7:3 8:21 36: 20 48:8,9 consultation [2] 101:20 266: 14 consultations [2] 124:4 306: 19 consulted [3] 118:5 127:4 144:13 consulting [1] 327:13 Consumer [2] 8:1 151:7 consumers [1] 235:21 contact [1] 27:18 contained [5] 46:6,15,16 78:</p>
---	--	---	---

<p>2 289:15 contains [2] 191:14 233:1 context [5] 15:12 222:21 244:1,17 327:16 continuation [1] 175:9 continue [8] 120:18 233:2 347:17 348:2,7 355:3 380:14 382:2 Continued [10] 4:1,13 76:20 251:7 272:21 298:9,17 346:4 359:13,16 continues [2] 134:19 139:2 continuing [3] 41:16 141:10 380:12 continuous [1] 86:22 continuously [1] 88:3 continuum [1] 160:16 contraindication [1] 167:21 contraindications [1] 166:14 contrary [2] 87:6 122:7 contrast [2] 114:8 280:9 contrasts [1] 114:3 contributed [1] 296:7 contributes [1] 67:15 contributing [2] 284:21 285:22 contribution [2] 180:6 358:2 contributions [2] 14:8 243:14 contributors [1] 16:5 Control [30] 7:21 30:4 38:5 39:13 46:19 52:6 59:20 63:19 66:1 85:15,18 87:10 88:5,10 92:1,21 115:7,8 158:1 187:4 190:18 191:5 210:11 225:22 270:3,4 284:12 285:14 286:6 309:4 controllability [1] 31:7 controlled [9] 17:5 40:3 76:13 86:18 91:21 116:7 155:4 226:10 298:7 controlling [1] 87:10 convene [1] 327:3 conventional [1] 376:20 conventions [1] 96:17 convert [1] 366:21 convince [1] 348:22 convinced [1] 271:14 convulse [1] 130:3 convulsion [2] 206:9 209:4 convulsions [18] 205:21 206:2 208:1,10,15 209:2,7,11,21 210:9,11,12 212:4 213:2 247:10,14 248:3,8 convulsive [5] 320:11,14 321:2,5 341:8 cooperation [1] 102:10 coordinated [1] 31:16 coordination [1] 268:15 coordinator [1] 34:21 copied [1] 250:19 cord [2] 18:6 218:6 core [1] 44:19 Cornell [1] 157:21 cornerstone [1] 142:3 coronary [2] 160:2 166:10</p>	<p>corpora [1] 231:3 correct [18] 171:11 173:13,14 176:6 178:19 180:3 215:19 306:6 309:18 315:20 327:15 338:7,9,10,11 339:13 347:20 358:11 correction [1] 331:11 corrective [10] 104:6,16 105:6 107:12,14 113:17 118:3 123:13,15 135:15 correctly [4] 178:2,12 317:16 360:6 correlate [1] 273:22 correlates [2] 265:13 293:3 correlation [2] 190:12 191:18 corresponding [1] 16:13 Correspondingly [1] 66:15 corresponds [1] 66:5 cortex [6] 51:20 191:1 225:3,5 261:2 273:17 cortical [1] 225:2 corticosteroidal [1] 58:2 cosmetic [1] 362:21 cost/benefit [1] 355:5 could [66] 13:10 21:14 22:10 23:17 26:22 35:7 87:16 90:5 144:18 145:8 148:5 149:13,14 159:6 162:9 169:15 170:10 171:6 175:4 178:11,13,16 181:12,18 182:4 184:12,20 199:3 201:7 203:15 206:3 213:10 215:3 216:14 217:3 219:5 220:7 223:19 230:1 234:5 258:18 302:7 305:7 311:16 319:12,13 320:15,16 335:2 337:3,13 339:9 340:21 344:19 345:6 351:22 354:6 361:9 362:5 363:10 364:3 367:15 373:14 374:2,22 383:3 couldn't [1] 119:8 Council [3] 4:8 235:10,12 count [3] 133:17 181:19 238:19 counted [6] 96:3,12,14,20 180:13,13 counterclockwise [1] 6:2 counting [1] 271:2 countries [6] 40:15 43:12,22 139:7 293:11 376:17 country [2] 295:8 335:1 couple [9] 174:14 218:5 238:8 247:4 284:1 309:9 311:19 352:10 369:22 coupled [3] 31:17 196:2 268:16 coupler [2] 53:4 54:17 coupling [1] 191:9 course [22] 19:19,21 21:6,15 46:11 63:16 80:9 97:16 101:15 103:2 106:4 126:15 135:8 138:4 140:22 227:4 279:17 295:13 340:22 373:17,21 376:7 court [1] 119:11 cover [3] 49:20 175:9 354:5</p>	<p>covered [1] 91:6 covers [1] 303:13 created [3] 247:4 248:11,15 CRESCENDO [8] 41:9 118:6 120:5 287:1 299:5 365:4 367:8 373:2 criteria [13] 31:19 38:8 101:21 124:19 128:13 177:2 252:8,17,20 275:8,10 308:22 309:1 criterion [1] 274:22 critical [5] 27:3 31:4 89:6 165:4 327:19 critically [1] 32:20 crossed [1] 114:7 crossover [1] 74:22 Crozz-Chester [1] 6:18 crucial [2] 382:8,12 crying [1] 276:21 crystal [1] 62:12 CSF [1] 273:21 cue [2] 95:19,21 culminating [3] 50:15 65:16 131:20 culmination [1] 67:12 culture [1] 64:21 cultured [1] 64:9 cultures [1] 64:15 cumulative [1] 294:21 curious [1] 323:4 current [21] 10:5 32:2 43:10 47:21 67:3 108:5 116:18 117:3 120:13 139:17 147:17 159:18 160:9 164:21 183:19 189:3 245:11 314:10 334:22 383:13,14 currently [24] 12:18 13:1 40:14 41:8,10 43:11 44:10,18 47:16 48:4,5 57:19 129:9 137:5 143:17 149:3 158:19 161:21 211:20 245:1 293:10 335:19 337:15 355:22 Curt [1] 6:6 Curtis [1] 2:25 curve [5] 56:9 197:2 208:7 330:13,14 curves [4] 54:22 80:8 196:7 331:5 cut [2] 20:11 22:14 cutoff [2] 258:22 279:8 cuts [1] 16:14 cutting [2] 22:15,16 cyclase [1] 195:19 cycle [1] 318:20 CYP3A [1] 43:6 CYP3A4 [1] 43:1</p>	<p>4 32:15 33:8 34:7 35:8,11 37:17 40:11 41:16 45:1,5,11 46:9 50:5 58:20 74:15 81:8 82:6 83:16 85:13 87:2 92:17,18 93:22 94:4 100:18 109:12 111:7 112:6,12 115:14 116:21 117:13 119:15 134:2 139:11,21 143:5 144:1 156:10 165:20 169:6 171:9,14 172:6 173:3,8,18 176:6,6 177:4 179:8 182:18,19,20,21 205:3,8 207:8,15 213:4 215:7 219:1 227:7 228:6 232:10,17 234:2 246:4,10 247:1,11 253:19 254:14 256:2,6 257:5,8 258:12 260:8 263:7 267:15 269:21 276:5 282:6 284:10 291:22 293:22 294:2,5 295:10 296:10,11 303:3 307:12,19 309:8,11,14 311:12,22 314:9,16,19 319:22 325:4 327:10,16,17 328:6 333:6 334:17 335:19 337:15 340:19 341:10 342:6,17,19,21 349:7,7,8,12,13 350:5,6 351:19 353:18 354:10,20 355:6,17,20 356:21 357:12 358:13 361:11 362:7 364:5,14,17 365:2,3,6,13,16 366:13,15 367:14 370:22 372:20 373:11 375:5,7,14 376:12 379:16,19 382:10 383:1,13,14 385:13 database [14] 40:2,21 106:5 114:6 132:8 134:10 182:20 256:4,20 264:16 269:6 282:18 286:15 294:19 databases [2] 20:9 129:14 dataset [6] 257:10,16 277:13 289:15 355:22 379:21 datasets [6] 257:9,11,15 258:20 281:18 289:16 date [11] 121:15 144:7 232:8 256:21 257:6 258:22 267:13 268:2 286:13 293:15 307:15 dates [3] 50:11 148:10 294:21 Davis-Bruno [30] 2:24 3:28 6:14,14 11:18 185:4,15,19 215:20 216:6,14,18 217:2,8 218:4,16 219:7 220:3,14,16 221:2 234:22 247:3 249:9,15,17 250:5 269:21 323:11,14 day [8] 5:15 12:1 17:19 39:22 94:18 166:12 169:20 266:8 days [16] 42:21 63:8 64:15 127:20 128:1,5 134:5 167:6,9 230:13 258:1,5 266:9 268:7 309:9 311:19 dead [3] 24:16 25:2 119:8 deal [11] 187:2 189:21 203:5 237:16 304:2 306:13 325:22 371:7,19 376:4,8 dealing [7] 24:8 49:8 146:14 151:17 307:7,10 329:21 death [3] 65:17 217:17 299:12 deaths [3] 20:22 100:13 233:</p>
--	---	---	---

D

D [4] 2:5,18 5:1 222:1
daily [7] 42:8 70:12 204:18 206:16 217:10,14 252:21
damage [1] 224:18
Dan [1] 127:4
dangerous [1] 246:6
dangers [2] 333:20 336:11
darned [1] 380:5
data [175] 12:18,21 13:1 18:15 20:3 27:1,2 28:8,11,12,20 31:

<p>10 debatable ^[1] 184:2 debate ^[1] 229:20 deceive ^[1] 316:7 December ^[2] 258:22 311:15 decided ^[1] 279:13 deciding ^[1] 373:14 decision ^[10] 119:12 157:7 166:6,7,13 222:18 241:7 246:12 273:20 371:22 decision-making ^[1] 243:21 decisions ^[1] 235:22 declare ^[1] 327:8 decrease ^[27] 62:17 67:13,13 72:20 75:5,6 86:22 87:1 88:3 177:8 178:22 179:7,17,22 192:8 197:1 200:9,10,11 201:3,8 202:7 203:7 231:3,4 322:15 357:17 decreased ^[12] 63:19 67:17 83:18,20 87:5 88:7 91:2 202:1,5,8 213:6 231:6 decreases ^[6] 58:8,9 62:15 76:6 68:8 209:5 decreasing ^[7] 25:18 62:15,16 67:5 174:9 177:14 193:12 deduced ^[2] 349:2,3 deeming ^[1] 116:7 defective ^[2] 52:2 65:13 defects ^[2] 231:7 381:3 deficiencies ^[1] 260:13 deficiency ^[1] 65:14 define ^[2] 16:11 244:1 defined ^[8] 139:9,12 159:11 167:15 168:16 274:16 279:7 377:10 definite ^[1] 109:22 definitely ^[7] 110:1,4 111:5 119:21 121:15 283:7,14 definition ^[4] 23:11,12 24:15 30:11 definitions ^[3] 366:13 375:19 381:15 definitive ^[2] 340:20 362:7 Degge ^[1] 327:12 degraded ^[1] 188:10 degrades ^[1] 62:13 degrading ^[1] 51:7 degree ^[3] 253:16 278:13 362:8 degrees ^[1] 382:18 delay ^[2] 169:15 268:10 deliberate ^[1] 37:10 delighted ^[1] 331:18 delineate ^[1] 32:11 delivered ^[1] 171:22 delivery ^[2] 201:1 245:13 delta-9 ^[1] 50:11 demand ^[2] 51:3 188:7 demographics ^[2] 77:13 86:7 demonstrate ^[4] 199:8 205:20 209:1 214:14 demonstrated ^[6] 72:5 135:11 138:7,17 164:4 209:11 demonstrates ^[1] 72:18 demonstrating ^[3] 25:22</p>	<p>145:13 197:3 demonstration ^[3] 52:9 65:3 203:10 demyelating ^[1] 239:5 denominator ^[1] 314:12 density ^[3] 191:6,9 261:1 deny ^[1] 356:11 departing ^[10] 13:18 DEPARTMENT ^[4] 1:1 9:14 14:21 303:8 depend ^[1] 181:9 dependent ^[3] 209:16 211:13 239:9 depends ^[2] 196:3 197:13 Depicted ^[1] 193:2 depicts ^[6] 190:10 197:2 256:4 265:10 275:15 348:13 depolarization ^[2] 192:2,19 depressed ^[31] 24:22 103:9 117:22 118:13 150:1 228:18 266:7 275:14 276:14,16 277:18 279:12 280:3,7,11 282:4,10 287:22 288:6,18 290:9,14 292:12 293:16 317:22 318:2,6,18 351:3 378:22 380:3 depression ^[110] 11:11 12:14 28:8,10 33:4,5,12 34:3,15 101:19 102:3,6 108:3,8,13 113:20 118:2,10,17 135:12,19 137:16,20,22 139:16,17 140:11 143:3 144:20,21 145:5,10 148:12 149:9 150:19 151:3 153:5,17 154:15 165:22 166:2,20 167:4,6,14,20 168:21 171:17 180:7,21 181:3,19 200:14 219:6 227:17,20 228:5,7,8,15,21 237:11,13 238:3 239:21 255:20,22 268:13 273:6,15 274:6,12,16,16,18 275:17 276:16 279:3,18,22 280:2 290:6,7,21 291:6 292:14,15 293:16 297:13 308:7 310:5 318:12 329:4 346:8,9,10,17 347:12 350:6,21,22 354:12,18 357:2 361:6 366:10 377:20 378:2 379:4 380:8 depressive ^[45] 33:6 47:14,16 48:3 99:7 101:6,16 103:20 104:2,13,15 105:3,5,8,9,14,15 106:4,13,20 107:1,13,19 108:4 113:9,14,18,21 119:3 122:9 123:9,11 147:4,5,14,15 148:17 183:21 184:4 187:9 219:8 226:14 275:21 289:5 290:17 depressive-related ^[1] 107:7 Deputy ^[2] 6:6,10 derivatives ^[2] 188:3 190:1 derive ^[1] 251:22 describe ^[3] 141:14,18 302:19 described ^[5] 179:10 196:16 197:12 348:10 373:22 describes ^[1] 230:13 describing ^[1] 15:16</p>	<p>description ^[2] 304:3 320:20 descriptor ^[1] 319:9 deserve ^[3] 245:12,18,19 design ^[7] 39:4 74:22 76:14 85:22 206:17 370:22 381:5 designed ^[5] 27:5 29:3 75:19 84:9 218:8 designs ^[1] 256:11 desirable ^[4] 199:12 200:2 214:17,19 desired ^[4] 200:9 212:7 214:3 298:19 desperate ^[7] 236:14 334:10 353:1,1,1 362:20 363:1 despised ^[1] 243:2 Despite ^[9] 63:9 255:21 256:19 265:1 266:14 272:19 275:10 342:4 380:6 despondency ^[1] 119:5 detail ^[6] 16:5 40:8 183:19 247:9 333:21 362:15 detailed ^[4] 143:2 372:5 375:21 377:1 details ^[5] 5:18 142:14 144:17 287:11 321:16 detect ^[1] 167:14 detectable ^[1] 54:20 detection ^[1] 153:17 deteriorating ^[1] 179:3 deterioration ^[1] 178:8 determination ^[1] 300:7 determine ^[5] 57:13,16 348:1,6 375:1 detrimental ^[2] 51:13 60:12 develop ^[11] 106:1 167:14 169:13 181:3 312:11 318:6,7,10,13 340:13 368:14 developed ^[13] 19:21 29:7,17 38:2 51:17 54:14 109:13 153:17 183:7 252:4 270:1 313:22 318:8 developing ^[7] 60:16 70:22 160:1 168:15 169:9 244:19 377:5 Development ^[23] 36:22 38:4,18 39:9 40:3,10 41:3 48:10 69:3 72:17 74:14 93:4,14 134:18 204:8 205:9 211:20 212:19 231:17 243:17 322:4 357:1 370:7 developmental ^[1] 56:18 deviation ^[1] 291:15 device ^[2] 162:22 163:9 devoid ^[2] 64:22 224:11 diabetes ^[90] 37:5 39:7,12 40:7 41:14 43:19 44:11 50:4,7 62:1,3,6 65:16 68:8,17 69:13 70:3,5,7 72:17,18,21 73:5 74:3 76:4,8,10,12 78:21 81:1 82:15 84:3 85:15 86:11,15 88:18 91:20 92:9,21 93:4,14,19 95:9,15,18,22 98:4 99:10,13 100:9,12,15 110:10 112:12 113:1 120:11 121:16 124:8 138:13,22,22 147:3 159:4,18,19 160:1,6,10,22 168:15 169:4,9,13,17 238:14 242:6 244:9,</p>	<p>13 245:9 253:6,10 255:17 264:21 328:18 330:6 331:18 346:14,14 364:3 381:22 diabetic ^[9] 39:15 85:21 86:7 87:9 124:15 135:5 256:9 265:2,7 diabetics ^[6] 70:4 85:17 100:1 256:15 265:9 297:22 diagnose ^[1] 142:5 diagnosed ^[3] 128:21 147:6 238:22 diagnoses ^[1] 123:2 diagnosing ^[1] 239:2 diagnosis ^[11] 47:15 86:16 101:21 108:4 127:2,6 147:15 268:10 306:21 320:12,22 diagnostic ^[1] 128:13 diagram ^[1] 154:1 dialog ^[1] 154:8 dialogue ^[3] 149:1 152:7 154:16 diaphoresis ^[1] 123:19 diarrhea ^[1] 99:1 diary ^[2] 153:19 155:22 diastolic ^[1] 253:15 Dictionary ^[2] 276:6 349:4 did ^[69] 16:9 19:2 21:17 25:20 26:22 28:7,11,12,14,16 40:13 41:2 104:7 106:14 113:11 116:2,7 122:6 125:14 128:12 144:12 145:7 155:20 156:2,14 169:12 174:21 175:19 181:11,21 184:5 218:13,20,21 279:20 280:1,7 289:17 291:13 300:19 305:6,10 306:1,18,19 308:3,10 309:1 312:1 315:4 316:20 318:12,17 320:5,19 321:16,21 322:21 323:13 324:18 325:4 326:6,7 336:15 341:8,12 346:5,7 352:19 didn't ^[17] 22:10,18 67:2 132:4,5 177:4 183:9 218:13 219:4 238:15 254:18 292:17 312:13 313:15 321:15 331:1 368:18 die ^[8] 23:20 24:16 30:18 35:14 36:1,2 120:7,9 diet ^[19] 43:17 63:14,21 73:6,15 76:19 82:13 91:16 146:20 151:15 154:11 161:18 169:8,13 235:13,14 238:16 252:22 253:2 dietary ^[2] 71:16 161:14 diethypropion ^[1] 229:8 differ ^[2] 96:17 258:17 difference ^[39] 27:20 79:11 90:4 98:21 99:1,4 103:11,15 105:2 106:8 107:16 108:6,10 114:10 124:12,14,20 125:8 179:17,19,20 180:1 239:22 259:17 278:17 306:17 310:4 315:18 324:3,4,8,10,18 325:13,14,18 339:10 344:21 360:6 differences ^[5] 97:6 121:18 179:11 214:2 369:20 different ^[34] 16:20 26:8,10</p>
--	---	---	---

<p>85:20 86:1 87:16 90:15 92:10 103:16 106:17 107:10</p> <p>116:16 158:18 177:16 179:4 191:16,16 247:1 256:12 257:17 261:11 262:1 263:20 274:21 277:11 279:6 302:11 303:13 306:14 331:6,8 345:16 370:18 377:14</p> <p>differential [1] 28:2</p> <p>differently [1] 130:14</p> <p>differing [1] 55:6</p> <p>differs [3] 111:9 114:16 212:5</p> <p>difficult [10] 57:12 80:22 162:14 257:12 302:22 306:21</p> <p>307:2 327:17 372:10 379:17</p> <p>difficulties [6] 17:14 118:18 124:2 125:7 260:17 280:12</p> <p>difficulty [4] 17:3 163:16 258:2 306:13</p> <p>dilation [1] 163:6</p> <p>dilemma [1] 367:21</p> <p>dilutes [1] 116:8</p> <p>diminish [1] 228:19</p> <p>diminished [1] 357:21</p> <p>direct [6] 151:7 201:8 223:6 296:4 341:2 352:19</p> <p>directed [3] 141:5 366:6 369:13</p> <p>direction [5] 61:5 165:8 331:3 354:15,19</p> <p>directions [2] 31:22 178:20</p> <p>directly [4] 210:3 233:15 340:7 367:7</p> <p>Director [7] 4:4,7 6:6,8,11 7:13 157:22</p> <p>disappointing [2] 333:10,11</p> <p>disappointment [3] 71:12,13 147:22</p> <p>disclosures [1] 15:15</p> <p>discontinuation [20] 98:5</p> <p>105:6 107:12 125:16,20 136:15 148:19 173:1 175:10 229:22 232:13 268:8 273:11 280:15,17 282:1 346:2 378:19,21 379:11</p> <p>discontinuations [3] 123:10 125:21 261:18</p> <p>discontinue [4] 79:16 172:20 173:15 181:1</p> <p>discontinued [16] 79:12 103:4 104:16 118:13 125:13,15 126:1 174:1 180:12 266:6 268:20 270:18 275:3 290:16 378:14 379:19</p> <p>discontinuing [1] 167:9</p> <p>discordance [1] 317:17</p> <p>discovered [1] 52:16</p> <p>discovery [3] 50:10,11,16</p> <p>discrepancy [6] 28:19 171:13 311:11,11 317:19 368:16</p> <p>discriminate [1] 35:20</p> <p>discriminated [1] 243:1</p> <p>Discrimination [7] 4:9 70:13 235:10 236:3,6,7,8</p> <p>discuss [18] 12:12,20 13:9 39:19 101:7 127:7 128:9 139:20 140:15,17 191:10 313:16</p>	<p>323:15 327:3 328:18 329:2,9 336:2</p> <p>discussed [20] 18:12 40:8 41:17 79:15,18 97:11,20 109:15 121:5 128:11 138:18 174:22 190:16 191:21 194:8 195:5 295:21 297:19 312:10 385:3</p> <p>discussing [5] 5:18 12:2 44:7,15 219:4</p> <p>Discussion [27] 4:16 5:13 10:1 12:6,7,11 27:4,11 47:18 51:15 95:8 112:11 137:14 140:22 186:3,5,10 224:13 299:22 315:7 328:16 329:1 336:6 340:6 347:17 369:15 385:4</p> <p>discussions [6] 9:19 11:10 59:18 245:17 369:22</p> <p>Disease [40] 7:21 47:8 70:21 73:13 85:8,9 122:8 125:3 141:21 142:3 144:4 146:17,18 151:5,13,14 152:18 153:10 158:17 159:5,18,19 160:2,3 166:10 236:22 244:9,10,19 265:1 270:14 274:15 299:9 303:16 304:3,8 317:13 365:1 368:13,15</p> <p>diseases [3] 51:14 160:11 161:5</p> <p>dishonest [1] 230:21</p> <p>disorder [24] 17:18,21 106:13,20 113:9,9,21 123:18 128:1,14 135:19 184:5 228:10 263:17 264:9 276:17 280:8 293:17 313:22 318:18 319:16 341:8,14 350:9</p> <p>disorders [77] 33:7 47:14,16 91:3 98:19 99:2,5,7 101:6 102:15 103:9,20 104:2,14,15 105:4,5,10,14,15 106:2,4 107:2,10,13,19 108:5 113:14 122:9,18 123:1,8,9,11 147:4,5,14,16 148:17 166:2 167:2 179:10,16,21 183:21 227:20 262:4 264:2,3,15 273:16 274:7 275:14 276:9,12,15,17,20 277:18,20,21 279:13 280:3 282:3,4,5,7 290:14,17 291:6 303:14 304:5 305:18 317:22 318:2 341:6,21</p> <p>disorientation [1] 264:8</p> <p>disparate [1] 374:22</p> <p>dispensed [1] 153:11</p> <p>dispersed [1] 231:20</p> <p>displace [1] 197:18</p> <p>display [1] 156:4</p> <p>disproportion [1] 358:2</p> <p>disproportionality [1] 289:17</p> <p>dispute [1] 17:20</p> <p>disrupting [1] 207:16</p> <p>dissociative [3] 313:14,21 320:17</p> <p>distal [1] 304:6</p> <p>distinction [2] 50:19 55:17</p> <p>distinguish [2] 36:3 379:10</p> <p>distinguishing [1] 104:11</p> <p>distress [1] 91:8</p>	<p>distributed [2] 220:4,20</p> <p>distribution [4] 190:11 198:18 202:22 204:1</p> <p>disturbance [6] 127:20 128:5 213:16 264:8 305:20 342:7</p> <p>disturbances [16] 103:10 200:5 202:16 262:22 275:14 276:15,17,20 277:21 279:13 280:8 282:4,5 297:14 318:1,3</p> <p>divergent [1] 368:1</p> <p>diverse [1] 225:12</p> <p>diversity [1] 382:7</p> <p>divided [5] 208:13 248:14 249:13 250:4 344:6</p> <p>Division [10] 6:9,15 7:13 13:12 45:8,9 185:16 224:5 263:5 282:20</p> <p>division's [2] 251:12 252:19</p> <p>dizziness [16] 99:2 124:11 126:4,4 136:12 154:21 262:13 268:13 293:17 301:10,11,14,19 303:12 342:2 351:10</p> <p>dizzy [1] 374:18</p> <p>DMC [1] 137:1</p> <p>do [113] 6:5 12:17 13:1 18:22 19:15,15 20:8 21:20 23:8 29:2 35:13 56:11,16 57:19 58:13 81:2 103:15 115:8 133:4,7 137:1,4 143:12 145:13 149:18 160:17 166:11 171:3,18 173:4 174:3,4 178:12 181:5 185:3 197:4 218:5,13 219:21 223:12 224:7 232:20,21 235:2 237:2 240:14 241:4 249:7 287:11 294:11 298:18 300:11,19 302:5 304:1,10 306:1 307:19 308:3 313:13,13 314:3,11,12,17 316:18 317:20 320:5 321:16 325:4 327:9 330:3 331:1 333:9 335:7,18 336:1 337:14 339:1,7 342:2,3,6,9,13 346:7,8 347:6 348:22 349:7 351:18 353:10,14 361:8 366:12 367:21 372:22 373:10,12 374:14 376:5,22 377:16 378:11 381:4,7,12,17 382:14 383:4,6,14 385:11</p> <p>doctor [1] 266:22</p> <p>doctors [1] 353:5</p> <p>document [7] 41:10 156:22 230:12,22 311:18 315:16 349:3</p> <p>documentation [3] 102:21 110:16 376:2</p> <p>documented [2] 102:16 342:10</p> <p>documents [5] 38:4,12,17 39:10 352:8</p> <p>does [32] 16:8 23:22 27:8,9 31:3 43:5 56:1 60:7 113:3 148:21 233:14 235:12 239:6,17 241:2 247:14,20 249:4 297:6 302:5 314:19 315:1 319:7 324:21 330:9 332:17 339:16 17 340:16 341:16 345:15 382:9</p>	<p>doesn't [7] 33:13 161:19 248:3 304:2,10 315:16 354:22</p> <p>dog [3] 206:3 212:21 218:21</p> <p>dogs [2] 204:13 205:18</p> <p>doing [9] 23:15 150:6 239:17 258:7 287:18 307:6 316:9 334:14 360:20</p> <p>Dom [3] 219:3 349:16 377:13</p> <p>domain [2] 91:7 161:12</p> <p>domains [2] 91:10 92:15</p> <p>Domenic [1] 7:8</p> <p>Dominic [3] 2:12 349:15 377:12</p> <p>don't [65] 28:21 30:2 34:5 35:10 57:18 132:22 153:1 158:19 159:19 172:1,10 173:10 175:20 182:7 200:19 216:4,6 217:18 220:5 232:20 239:12 240:10,18 241:7 265:19 277:9 291:21 307:12 314:15 317:18 319:21 321:11,17,17,18 324:9 325:3 335:7,7 336:11,22 339:4 341:1 342:3 347:4 349:6,8,11 350:22 351:2,20 354:18 355:15 356:10 361:10 364:9 365:2,2 368:22 370:15 371:13 377:15,17 379:6 381:11</p> <p>done [27] 21:1 26:11 134:9 172:17 204:14 216:8 224:3 229:3 232:22 236:9 237:12,20 257:22 307:9 308:21 316:7 332:7,9,10 334:21 335:14 345:13 360:7 368:9 371:5 372:1 380:18</p> <p>dopamine [2] 194:16 195:11</p> <p>dosage [1] 73:22</p> <p>dosages [1] 256:13</p> <p>dose [57] 39:21,22 97:2 110:22 111:1,20,22 112:1 115:5,16 119:1 126:19 132:16 134:5,7 196:4,7 197:15 205:18 207:3 208:4,9 209:4,12,16,19,19,22 211:2,13,17 213:13 231:5 239:8 247:13,18,18,22 248:3,15 249:16 250:7,7 270:3 309:10 311:20 316:12 339:4,8,13,18,18 340:13,14 344:10 361:20 370:2</p> <p>dose-dependent [2] 211:11 213:14</p> <p>dose-ranging [1] 75:9</p> <p>dose-related [1] 217:3</p> <p>dose-response [1] 197:2</p> <p>dosed [1] 61:3</p> <p>doses [16] 75:10,12,19 86:2 100:13 126:18 131:6,20,21 133:5 208:19 210:7,18,22 231:5 270:2</p> <p>dosing [3] 209:14 217:10 270:7</p> <p>dossier [2] 44:13 139:10</p> <p>dots [1] 58:6</p> <p>double [2] 169:12 361:20</p> <p>double-blind [3] 76:16 109:9 120:2</p> <p>doubled [3] 106:13,15,16</p>
---	--	--	---

<p>doubling ^[4] 281:21 297:11, 14 354:21</p> <p>doubt ^[3] 230:10 232:3 332:5</p> <p>down ^[21] 23:6 36:2 54:8 61:19 103:12 145:9 150:1 209:12 238:21 241:21,21 262:19 283:6 291:19 301:21 325:7 330:16 333:14 337:2,5 363:13</p> <p>downward ^[3] 96:21 97:3 110:21</p> <p>DPP ^[2] 169:6 238:13</p> <p>DR ^[512] 5:3,5 6:1,4,4,8,8,10, 12,14,17,20,22 7:4,6,8,12,16, 18,20,22 8:2,4,6,8 9:1,5,8,10, 12,15 10:9,10,13,16 11:6,18 12:1 13:17,20 14:5,15,18,19 15:2,7 16:1,2,2 23:13 29:13 33:16,16,18,19,21 34:8,12,20 35:2,6,10,19,22 36:7,9,14,18 37:8,14,17,19,22 39:4 40:10 42:5 45:21 49:3,6,10,12,12 68:22,22 69:1,4,6,8 88:14 93:1,1,2,6,8,8 94:7 96:5 97:20 98:10 108:14 109:14 110:2 111:20 113:9 121:5 122:13 127:4,6 135:21 136:10 138:18 139:15 140:2,2 147:21 157:19,20 158:3,5,8,10,12 170:7,9,9,13,15 171:6,6,8,12, 19 172:10,12,12,15,15 173:9, 14,17,20 174:2,7,11 175:2,3, 6 176:10,11 177:18,19,20 178:18 179:10 180:4,8,9,10, 17,17,17 181:2,2,13,16,21 182:3,3,4 184:9,9,12 185:4, 11,15,19 197:8 198:16 215:14,16,20,22 216:6,10,10,11, 14,16,18,21 217:2,5,8,19,21 218:4,11,11,12,16 219:3,7,10, 10,11,13 220:3,10,14,15,16, 21 221:2,3,3 222:2,15 223:18 224:1,3 234:22 235:7,7 243:6 246:1,15,18 247:2,3 249:5, 9,11,12,15,16,17 250:2,3,5,9, 13,16 251:2,6,9 269:21 282:22 283:1,12 293:20 294:2 296:22 300:2,3,5,13,21,21, 22 301:1 302:7 303:2,5,19, 22 304:12,16,18 305:14,16 306:6,22 307:4,14,14,15,21 308:2,3,12,16,17,20 309:20 310:1,2,20 311:2,10,14,16,18 312:3,7 313:11,11,12 314:7,7, 8,15 315:4,6,22 316:10,15,16, 17,17,20 317:8,10,10,11,21 318:19 319:12,15 320:2,4,4,6, 7,8 321:6,7,10,10,11,17,20 322:2,3,21 323:9,11,11,14,21, 22 324:11,11,14,15 325:12, 17,20 326:2,2,11,22 327:11, 12 328:17,22 329:11,14 335:16,16,21,22 336:9 337:8,13, 17,18,19,21,22 338:1,4,12,16 339:1,3,11,14,22 340:3,4,5,7 342:13,16,18,20,22 343:1, 1,20,21 344:2,17 345:3,6,8,9,</p>	<p>18,21 346:18,20,21,21 347:1, 11,14,17,18 348:10,16 349:14,14,16 351:17,20,21 353:22 354:2,3,4,6,8 355:21 356:1,3,3,4 358:11,12,14,15,16 359:3 362:2,4 364:11,13 365:18,20 367:17,19 369:7,8,9,11, 12 370:10,15 371:16 372:13, 14,18 373:13 374:11,11,12, 15 375:16 376:5,11 377:7,9, 11,13 378:8,17,18 379:9,17, 22,22 380:1,11,16 383:4,20, 21,21,22 384:1,1,1,3,4,5,7,7, 8,9,9,10,11,11,12,13,13,14, 15,15,16,17,17,18,19,19,20, 21,22 385:9</p> <p>dramatic ^[1] 209:13</p> <p>dramatically ^[1] 25:19</p> <p>dream ^[1] 71:10</p> <p>drill ^[1] 301:21</p> <p>drive ^[1] 55:3</p> <p>driven ^[6] 23:12 121:17 179:9 262:12 263:13 264:5</p> <p>driving ^[2] 179:19 180:1</p> <p>drop ^[5] 172:2,5 174:21 293:7 379:7</p> <p>dropout ^[19] 171:1,5,10,15 174:12,13,21 175:7,16,19,20, 21 176:1 229:16 340:11 359:6,20 362:10 379:13</p> <p>dropouts ^[5] 229:18 230:3 254:4 353:13 378:11</p> <p>dropped ^[5] 145:12 173:12 358:21 359:11,14</p> <p>dropping ^[1] 172:6</p> <p>Drs ^[1] 14:3</p> <p>DRUG ^[116] 1:2,3 6:7 21:9 27:9 28:3 36:20,22 39:3 41:3 61:2 78:19 88:2 138:6,6 165:16 168:17 171:22 174:3 182:9, 17 185:16 213:8 216:5 224:9 226:8,12 227:3,17 229:21 231:9,21 232:9,14 233:2 234:7,15,18,20 235:5 237:17,21 238:4,9 239:10 240:2 241:6, 8 242:12 245:10 246:10 249:13,14 252:7,15 256:13,13,21 258:1 268:8 280:16 289:11 291:3 294:6 298:6,8,11 312:9 313:10 314:6 319:4 322:12, 18 327:13,15 330:8 331:3 332:16,22 334:4 335:13 337:3,8,11 340:15 343:8 348:14, 18 349:13 352:2 359:5,10,21 360:5,17 361:12,16 362:5 363:10,22 364:19,21 366:1 370:16 376:15 378:21 379:2, 3,5 380:9,14,15,19 381:17 382:16,20</p> <p>drug's ^[2] 252:9 337:15</p> <p>drug-associated ^[2] 252:10 298:13</p> <p>drug-drug ^[1] 43:6</p> <p>drug-related ^[1] 288:12</p> <p>drug-review ^[1] 246:5</p> <p>Drugs ^[30] 5:4 13:22 38:4,18 71:18 73:17 160:22 161:11</p>	<p>166:20 167:5 213:21 229:10 250:4 252:6 253:4 254:7,7 294:13 295:13 309:4 314:20 328:7,10 330:22 331:14 333:9 337:10 382:9,17 385:10</p> <p>DSM-IV ^[1] 101:21</p> <p>dual ^[1] 67:14</p> <p>due ^[22] 57:14 60:16 63:11 70:13,17 114:17 126:1 176:2 179:20 216:12 228:17 233:9 254:13 261:19 266:7 275:7 282:2 289:10 290:16 292:2 293:7 360:22</p> <p>durability ^[2] 84:6,14</p> <p>duration ^[19] 31:7 36:4 38:6, 10 39:3,22 77:4,7 209:4,14 211:13 217:10 232:8 239:9 259:10 269:13 299:10 310:16,19</p> <p>durations ^[3] 204:15 208:20 256:12</p> <p>duress ^[1] 335:3</p> <p>during ^[51] 40:3 42:15 44:8 46:3,10 52:13 75:3 80:15,18 88:16 94:21 101:15 102:4 103:2 115:1 126:11 128:22 134:4 137:22 142:19 148:12 149:22 156:12 171:10 174:8 175:22 176:1 182:16 183:13 206:17 227:3 230:6 237:3 253:2,21,22 254:1 257:20 258:4 262:2 271:5 272:19 273:7 277:5,10 279:16 281:8 284:9 286:16 322:20 331:20</p> <p>Durleman ^[6] 172:13,15,15 173:14,20 310:2</p> <p>dying ^[1] 242:17</p> <p>dynamic ^[1] 145:19</p> <p>dysarthria ^[1] 263:17</p> <p>dysesthesia ^[1] 262:18</p> <p>dysfunction ^[8] 200:15 206:20 212:4 214:6 226:8,12 263:18 288:18</p> <p>dysgeusia ^[1] 262:19</p> <p>dyslipidemia ^[9] 43:19 65:15 70:21 76:10 78:12,15 84:4 91:19 147:3</p> <p>dyslipidemic ^[2] 78:19 83:3</p> <p>dysphonia ^[1] 263:16</p> <p>dysregulation ^[1] 199:16</p> <p>dysthymic ^[1] 276:16</p>	<p>earmarks ^[2] 103:16 104:12</p> <p>ease ^[1] 242:10</p> <p>easier ^[1] 229:2</p> <p>easily ^[2] 31:17 321:22</p> <p>easy ^[2] 237:8 381:3</p> <p>eat ^[2] 119:8 174:3</p> <p>eating ^[1] 227:20</p> <p>echo ^[1] 385:9</p> <p>ECS ^[12] 164:5 186:4,14 189:20 196:13,20 197:1 199:10, 14 200:1 202:6,12</p> <p>editor ^[1] 158:5</p> <p>editorial ^[1] 288:16</p> <p>educate ^[1] 151:13</p> <p>educated ^[2] 151:10 155:11</p> <p>education ^[7] 141:10,11 142:2,2 146:14 167:16 168:20</p> <p>educational ^[4] 145:16 155:7 168:3 236:7</p> <p>EFC ^[3] 284:7,12 285:13</p> <p>effect ^[62] 21:13 34:3 55:11 57:10 59:4 60:5 64:2,5 68:9 75:4,14 82:12 83:15,22 84:14 86:20 89:12,18 90:5 172:8,8 196:2 197:13 200:9 201:4,16,16,19,22 202:2,12,12 203:11 205:12 208:4 209:13 210:4,10 212:8 214:4 232:10 234:7 247:12 248:14,22 249:20 252:9 253:13 255:12 259:5 296:4,5 298:13,22 307:16 325:16 326:16 330:18 332:4 349:1 360:21 368:5</p> <p>effective ^[14] 71:20 74:6 88:1 145:13 151:16 169:21 197:9 232:14 245:20 252:7 297:5 322:19 345:11 356:7</p> <p>effectively ^[1] 288:3</p> <p>effectiveness ^[4] 140:18 145:6 152:14 230:3</p> <p>effector ^[1] 191:9</p> <p>effects ^[101] 27:17 43:1 52:18 55:18,19,21 58:1,21 59:8 60:4,14 61:1 65:8 67:16 68:11, 19 82:20 92:6 103:5 161:10 162:2 165:13 166:19 169:22 170:20 171:17 180:3 187:9, 10,14 194:5,9,10,17 195:14, 16,17,22 196:10 197:7,8,16 198:9 200:2,3 201:5,8,13,14, 15,15,21 203:7 206:10,19 207:12,16 209:9 213:3 215:9 218:15,16,22 220:2,8 225:9 227:3 230:12 232:6 233:17, 19 238:16 245:5 264:16 278:7 285:12 289:11,12 300:7 321:13 323:13,16,17,19 328:11 334:13 343:11 347:3,21 348:1,14 349:19 350:5 351:8 356:14 359:21 360:18 372:8 375:15 377:15 382:6</p> <p>Effexor ^[1] 183:11</p> <p>efficacies ^[1] 55:6</p> <p>efficacion ^[1] 57:20</p> <p>Efficacy ^[41] 3:16 4:14 11:3 37:17 38:7 47:1 49:18 69:5,7, 12 74:15 81:13 84:6 85:13</p>
--	---	--	--

E

E ^[7] 3:1 4:1 5:1,1 222:1,1,1

e-mail ^[1] 338:4

each ^[15] 5:10 36:5 98:8 105:19 152:8 153:11 155:11 177:13 237:4 255:2 314:13 327:4 334:16 381:22,22

eager ^[1] 246:7

earlier ^[20] 94:7 97:20 158:7 167:19 187:3,18 196:19 198:13 246:2 283:2 295:21 310:3 313:3 316:11 323:12 327:22 355:7 357:11 367:21 374:16

early ^[8] 65:17 66:9 134:2 141:17 142:9 183:8 290:16 329:17

<p>92:17 164:22 175:17 203:10 222:5 229:21 230:1,10 232:7 234:14 235:9 243:18 245:4 246:4 251:8,17 252:20 253:5, 19 256:9 308:15,16 322:5 337:9 350:1 355:11 357:16 efficiency ^[1] 191:10 efficient ^[1] 370:7 efficiently ^[1] 31:16 efforts ^[6] 32:6 242:22 272: 19 299:19 332:10 354:14 Egan ^[32] 2:26 4:15 6:12,12 12:1 185:11 222:6 250:13 251:6,9 296:22 300:3,5,13 302:7 304:12 306:6 307:21 308:3,16 309:20 313:11,12 315:22 316:15,20 317:21 319:12 321:7,17 323:11 324: 11 Egan's ^[2] 247:2 250:16 Egen ^[1] 316:17 Eight ^[2] 133:14 319:3 either ^[16] 63:14 73:21 77:10 78:12 84:18 114:21 115:11 150:7 195:9 199:11 208:6 218:21 267:7 283:14 326:6 382:16 elderly ^[1] 321:4 electronic ^[1] 20:8 elegantly ^[1] 348:11 elements ^[6] 45:11 140:8 147:18 151:22 154:3 156:17 elevated ^[2] 78:4 82:22 elicit ^[1] 197:16 elicits ^[1] 269:14 eligible ^[1] 343:7 eliminate ^[1] 372:16 Elizabeth ^[1] 224:4 eloquent ^[1] 300:4 else ^[8] 23:4 221:1 224:20 331:10 357:14 362:6 365:16 373:10 elusive ^[1] 224:9 Email ^[1] 386:2 EMDAC ^[1] 2:4 EMEA ^[4] 231:1 293:22 296: 10,13 emerge ^[1] 167:4 emerged ^[1] 61:12 emergence ^[1] 274:5 emerges ^[1] 122:1 emerging ^[1] 354:11 Emeritus ^[1] 6:21 emotional ^[5] 178:6,7 179:6 357:22 358:7 emotionally ^[1] 178:16 emphasis ^[1] 157:5 emphasize ^[7] 44:17 54:15 182:15 350:8 367:21 368:1 370:13 employed ^[7] 9:8,13 45:22 218:2 256:5 284:2,12 employing ^[1] 44:16 employs ^[1] 246:10 enable ^[1] 155:8 encompasses ^[1] 306:11 encountered ^[1] 57:9</p>	<p>encourage ^[1] 370:6 encourages ^[2] 223:1,11 end ^[15] 5:14 12:9 24:20 27: 21 115:2 127:8 130:18 150: 13 162:7 221:1 229:12 239: 17 266:12 280:21 379:12 ending ^[1] 24:17 endocannabinoid ^[55] 49:7, 21 50:3,10 51:7,10 57:18 59: 6,16,22 60:8,10 61:6,8,13 62: 6,10 65:3 67:21 68:6 158:21 163:22 186:4,14,19 187:1,7, 14,19 188:18 190:3,15 191: 22 192:3,10 193:1,4,5 194:4 195:15 196:12 199:10 200: 15,17 201:22 203:17,19 207: 16 211:10 213:16 214:15,19 269:11 292:9 298:2 endocannabinoids ^[31] 50: 17,20 51:5 53:5,8 58:4 61:16 187:21,22 188:2,6,13,17,20 192:6 193:18,20 194:11,22 195:18 196:5 198:3 201:14, 17,17 207:13,19 269:15 272: 17 273:13 331:7 Endocrine ^[5] 6:15 8:4 13:21 185:16 187:10 Endocrinologic ^[1] 5:4 endocrinologist ^[1] 14:3 endocrinologists ^[1] 159:6 Endocrinology ^[4] 6:9,11 8: 3 48:13 endogenous ^[14] 50:17 57: 11,15 67:22 186:3,15 187:20 195:18 196:5 198:3,13 201: 14,17 273:21 endogenously ^[1] 267:7 endpoint ^[1] 322:11 endpoints ^[5] 298:18 299:7, 15 356:15,16 energy ^[10] 13:15 63:9 68:1 118:17 164:2 186:20 187:4 189:19 200:22 243:3 engaging ^[1] 24:10 England ^[2] 240:6 288:16 English ^[1] 152:5 enhanced ^[3] 141:12 143:1 220:12 enjoy ^[2] 59:7 174:5 enjoying ^[1] 357:17 enjoyment ^[1] 174:9 enlisted ^[1] 334:16 enormous ^[3] 236:1,22 245: 15 enough ^[16] 22:11,21 23:7 24: 11 241:17 285:1,4 336:22 337:1,2 339:6 358:10 362:14 364:10 371:13 376:12 enriched ^[2] 190:19 191:3 enroll ^[1] 155:12 enrolled ^[10] 41:15 94:17 255: 7 266:5 275:11 279:11 281:4, 6 299:9 366:20 enrolling ^[1] 41:10 ensure ^[1] 222:18 entering ^[2] 128:21 328:6 entertain ^[1] 329:8</p>	<p>entire ^[5] 170:22 257:20 277: 5 286:14 359:5 entity ^[1] 319:19 entry ^[1] 275:22 environment ^[3] 235:21 301: 16 302:3 environmental ^[1] 244:5 enzyme ^[4] 62:13,15,16,18 enzymes ^[4] 43:6 51:3,7 192: 22 epidemic ^[3] 69:18 70:2 74:4 epidemiologic ^[2] 121:21 122:12 epidemiological ^[1] 287:18 Epidemiology ^[2] 48:22 143: 22 epilepsy ^[11] 129:7,9 130:3 136:19 137:6 139:19 149:10 270:15 320:22 321:1 340:18 epileptic ^[3] 320:21 341:9,12 epileptiform ^[1] 269:14 epinephrine ^[2] 60:2,4 episode ^[3] 320:17 341:9 375: 12 episodes ^[4] 48:3 99:17 118: 11 274:18 equal ^[4] 13:5 206:21 290:5 347:4 equally ^[2] 87:22 107:3 equals ^[1] 326:5 equivalent ^[3] 112:4 211:15 231:1 era ^[1] 50:9 Eric ^[11] 2:23 3:8 6:10 10:10 13:17 293:20 338:3 339:2,11 370:2 375:17 erosion ^[1] 163:6 err ^[1] 362:17 error ^[3] 18:5 360:13,13 esophageal ^[1] 166:8 especially ^[13] 43:19 138:4 154:15 166:1 176:2 196:6 257:12 258:4 265:19 312:13, 20 349:20 364:17 essential ^[2] 305:8 379:15 Essentially ^[3] 192:19 326: 20 351:16 establish ^[1] 121:3 established ^[4] 65:5 122:15 137:19 190:14 esteem ^[1] 70:14 estimate ^[10] 116:3,8,13 164: 22 259:5 264:18 265:11 285: 18 286:7 309:3 estimated ^[8] 33:9 54:17 69: 20 89:17 120:1,1 126:14 293: 12 estimates ^[5] 26:14,17 114: 11 265:14 293:5 estimation ^[1] 156:11 et ^[17] 19:4 20:11 27:17 28:10 31:7 35:12 36:4 149:14 154: 22 171:17,18 218:6,6 305:20, 20 353:3 378:16 ethnic ^[1] 368:11 EU ^[1] 44:10 EUDRA ^[1] 328:5</p>	<p>Europe ^[19] 43:12,16,20 44: 22 45:18 84:8 135:2 139:6 143:17 144:7 231:9 240:7 255:17 259:19 294:17,18 295:7 296:17 369:3 European ^[10] 45:5 144:10 215:2 231:1 293:15 314:9 327:10,17 368:18 377:8 Europeans ^[1] 294:7 evaluate ^[9] 155:3 234:14,19 258:18 269:4 276:3 322:15 331:22 382:7 evaluated ^[7] 41:4 119:15 128:12,14 138:7 162:10 322: 10 evaluating ^[4] 76:17 162:8 232:10 233:17 EVALUATION ^[25] 1:3 3:27 6:7 11:20 109:6 118:16 123: 4 127:7 129:5 138:1 145:7 150:8 158:14 167:20,22 168: 17 185:6,15,18 246:16 252:5 299:6 320:5 322:9 381:10 evaluations ^[1] 150:22 even ^[35] 8:17 16:10,12 21:11 24:4 27:7 61:21 132:18 145: 12 160:4,7 184:2 195:3 227: 6 228:22 229:1 236:8 241:8 242:9 280:22 287:14 296:18 316:14 321:18 333:4 341:10 354:22 358:21 359:10,13,19 361:2 367:11 377:17 381:18 even-handed ^[1] 348:17 event ^[43] 9:19 15:5 16:19 17: 15 20:12 98:19 107:5,20 110: 22 115:4 116:5 117:5 124:19 126:14,16,20 132:15 181:5 183:3 257:13 258:2 262:13 264:14 265:4 277:3,8 278:4, 12 279:16,19,21 280:7 281: 22 288:22 295:1,14 307:22 318:5,8,11,13 335:6 376:1 events ^[158] 12:13,15 17:4,6, 8 20:15,20,22 21:3,21,22 22: 9 25:10,12 28:16 29:4 30:2 32:12 45:21 79:17 94:3,22 95:10 98:4,6,14 99:10,12 100:6,9,22 101:3,4,10,17 102: 12 107:7,9 108:7 109:2,4 110:6 112:4,5,9 113:2,11,18 115:10 121:13 125:19,21 128:18 131:3,15 135:6 136: 11 142:5 153:7 154:14 159: 10,13 167:10 170:2 171:2 172:20 173:5,6,7 175:17 182: 1,13,15 251:21,22 257:10 258:7,13,14,21 260:2,5,6, 11,15 261:11,15,17,19 262:1 263:10,20 265:18 266:3 268: 17,19 277:9,16 280:14,16,21 282:2,2 284:16 286:9 288:12, 13,20 289:5,7 290:9 293:8 294:22 295:10,12,18 296:7,8 297:12,17,21 300:18 302:9 306:10 307:1,17 313:14 315: 14 316:5 318:15 324:20,21 328:8 329:4,5 340:9,21 343:</p>
--	---	--	--

<p>4 344:3 346:1,3 352:11 355:14 358:3 362:11,13 363:11 367:2 371:4,10,11,11,18,22 373:4 375:19,20</p> <p>eventually ^[1] 54:7</p> <p>every ^[10] 22:2 23:10 34:2 142:7 164:3 166:11 169:20 293:4 300:17 339:17</p> <p>everybody ^[10] 5:21 15:8 47:2 184:13 185:12 238:1 249:6 362:6 381:19 383:14</p> <p>everyone ^[2] 157:5 334:1</p> <p>everything ^[3] 30:10 106:16 365:16</p> <p>everywhere ^[1] 23:4</p> <p>evidence ^[15] 29:18 50:2 51:9 61:12 62:9 64:7 161:17 199:7 226:1 227:16 243:20 267:2 313:16 360:2 366:3</p> <p>evident ^[2] 202:21 224:13</p> <p>evocative ^[1] 130:1</p> <p>evolution ^[1] 381:20</p> <p>evolve ^[1] 382:3</p> <p>evolving ^[1] 298:3</p> <p>exacerbate ^[1] 341:3</p> <p>exacerbation ^[2] 268:7,21</p> <p>exact ^[6] 60:15 110:16 260:2 286:10 316:1 325:4</p> <p>exactly ^[15] 31:21 34:11 35:22 38:21 143:7 149:17 301:21 306:3 330:14 331:2,22 332:11 349:11 368:22 375:10</p> <p>exam ^[2] 266:20 307:8</p> <p>examination ^[2] 306:2 332:9</p> <p>examinations ^[1] 128:19</p> <p>examine ^[1] 210:4</p> <p>examined ^[2] 101:6 330:12</p> <p>example ^[24] 19:8 24:19 54:11 57:22 60:18 63:13 87:7 154:7 190:17 197:17 205:15 216:22 217:18 223:7 225:15 227:8 231:18 247:20 288:15 304:3 307:8 360:3 361:4 370:1</p> <p>examples ^[4] 17:11,14 19:6 224:15</p> <p>exceed ^[1] 338:21</p> <p>exceeded ^[1] 38:9</p> <p>exceeding ^[1] 252:11</p> <p>exceedingly ^[1] 334:10</p> <p>excellent ^[2] 25:20,22</p> <p>except ^[3] 77:15 302:2 341:2</p> <p>exception ^[1] 245:3</p> <p>excess ^[1] 227:6</p> <p>excitability ^[1] 207:18</p> <p>excitatory ^[3] 52:1 58:2 193:15</p> <p>exciting ^[2] 370:19 385:14</p> <p>exclude ^[6] 10:1 108:8,11 229:2 272:20 344:21</p> <p>excluded ^[12] 129:8 130:16 136:20 166:4 220:6 255:20 270:13 274:13 280:4 282:7 292:11 357:7</p> <p>excluding ^[7] 76:8,10 116:4 132:14 284:17 317:4 346:18</p>	<p>exclusion ^[7] 10:2 31:19 228:18 229:5 274:21 275:8,10</p> <p>exclusions ^[1] 20:15</p> <p>execute ^[1] 15:19</p> <p>Executive ^[1] 2:3</p> <p>exercise ^[12] 43:17 76:19 81:2 82:13 91:16 146:20 151:15 154:11 161:18 169:8,14 238:17</p> <p>exhibit ^[2] 288:4 291:5</p> <p>exhibited ^[2] 17:18 233:13</p> <p>exist ^[1] 51:1</p> <p>existed ^[1] 205:5</p> <p>existing ^[1] 127:19</p> <p>exists ^[2] 51:10 214:13</p> <p>exogenously ^[1] 267:7</p> <p>exotic ^[1] 54:16</p> <p>expansions ^[1] 245:7</p> <p>expect ^[12] 58:11 172:2 217:16 234:3 246:9 248:9 296:3 315:14 316:13 321:3 333:18 341:1</p> <p>expectancy ^[1] 244:8</p> <p>expectation ^[2] 79:14 353:12</p> <p>expectations ^[5] 72:4 148:4 171:20 174:16,19</p> <p>expected ^[14] 78:5 79:9 85:5,6 86:14 117:7 136:3 228:3 234:2 253:6,16 291:18 309:6 316:4</p> <p>expecting ^[1] 279:17</p> <p>expects ^[1] 246:5</p> <p>expeditious ^[1] 159:12</p> <p>expeditiously ^[1] 246:12</p> <p>expenses ^[1] 223:9</p> <p>experience ^[33] 33:9 35:2 44:7 45:17 93:12 109:17 116:18 121:14 134:8 135:1,20 137:1 139:8 144:7 167:3,10 173:5 175:4 179:9 205:5 211:19 247:21 273:2 277:2 282:8 291:5,13 294:8 313:21 314:10 360:19 364:5 376:19</p> <p>experienced ^[5] 127:20 180:21 277:7 280:6 352:21</p> <p>experiencing ^[8] 178:15 180:7 209:21 278:4 279:19 301:22 342:1 374:21</p> <p>experiment ^[10] 52:22 56:7 58:8 63:13 64:8,9,13 65:13 66:3,6</p> <p>experiments ^[2] 58:18 65:18</p> <p>expert ^[2] 171:22 233:11</p> <p>expertise ^[1] 14:10</p> <p>experts ^[11] 29:12,18 48:8,8,12 130:8 131:9,12 132:4 133:12 319:5</p> <p>explain ^[9] 13:8 89:14 178:13 198:1 217:4 247:8 284:2 293:21 302:1</p> <p>explainable ^[1] 328:9</p> <p>explained ^[9] 54:12 68:9 89:8,18 90:6 91:2 92:13 112:10 359:22</p> <p>explaining ^[1] 258:11</p> <p>explains ^[5] 289:22 290:3,13 328:3 361:10</p>	<p>explanation ^[5] 27:13 28:2 226:11 258:17 317:20</p> <p>explanations ^[1] 30:5</p> <p>explanted ^[1] 163:9</p> <p>explicit ^[1] 24:13</p> <p>exploratory ^[1] 89:13</p> <p>explore ^[2] 89:11 355:19</p> <p>explored ^[1] 291:9</p> <p>exposed ^[7] 94:9 95:13 97:12 117:19 270:1 342:5 367:3</p> <p>exposure ^[65] 40:21 43:4 94:16 96:2,3,10,12 97:12 117:3 118:9 120:1 126:14 134:21 205:14,17,19 206:1,5,11,22 207:2,4 208:6,6,12,14 209:18 210:1 211:2,6,16 212:2,7,9 213:1,5,6,12 215:5 217:14 247:17,20,21 248:1,4,7,14,20,21 249:1,2 250:1,6,8 256:13,18 257:6 310:19 311:2,6,7 338:17,18 364:15 366:22</p> <p>exposures ^[16] 199:20 200:8 204:19 205:22 208:11 209:7 211:15 212:14,20 213:8 214:1,3,22 217:15 248:13 249:22</p> <p>express ^[3] 14:7 246:13 326:19</p> <p>expressed ^[12] 56:4,6,8,8 176:13 191:15 208:4 213:4 247:11,19 248:12 257:3</p> <p>expressing ^[1] 176:7</p> <p>expression ^[4] 64:11,20 191:19 195:22</p> <p>extended ^[1] 232:18</p> <p>extending ^[1] 60:22</p> <p>extension ^[1] 46:5</p> <p>extensive ^[3] 123:22 134:19 183:19</p> <p>extensively ^[6] 42:2,13,18 49:6 186:22 189:20</p> <p>extent ^[5] 80:9 121:3 166:21 315:2 322:12</p> <p>external ^[2] 131:9 137:1</p> <p>extraordinarily ^[1] 226:7</p> <p>extraordinary ^[2] 240:7 330:5</p> <p>extrapolated ^[1] 343:6</p> <p>extrapolation ^[1] 352:15</p> <p>extreme ^[2] 162:7 355:9</p> <p>extremely ^[1] 363:15</p> <p>eye ^[3] 49:17 106:10 266:20</p> <p>eyes ^[1] 352:8</p>	<p>168:10,14 191:8 244:5 373:14</p> <p>facts ^[1] 184:7</p> <p>failed ^[2] 39:12 275:7</p> <p>fails ^[2] 24:3 71:5</p> <p>failure ^[2] 65:16 363:19</p> <p>failures ^[1] 71:5</p> <p>fair ^[2] 303:10 304:19</p> <p>fairly ^[4] 10:14 64:17 315:14 332:21</p> <p>fairness ^[1] 10:4</p> <p>fall ^[2] 173:10 336:11</p> <p>falling-down ^[1] 375:12</p> <p>falls ^[1] 351:11</p> <p>false ^[2] 20:16 28:21</p> <p>familiar ^[6] 5:22 34:14 48:14 150:20 302:20 330:13</p> <p>families ^[1] 152:2</p> <p>family ^[7] 141:7,22 148:15 150:17 152:11 154:18 266:22</p> <p>fantastic ^[1] 353:11</p> <p>far ^[6] 94:15 143:20 195:17 242:14 310:15 351:7</p> <p>fashion ^[4] 64:12 98:7 115:3 188:10</p> <p>faster ^[1] 108:19</p> <p>fasting ^[3] 87:4 88:6 297:7</p> <p>fat ^[7] 61:20,20 63:21 67:13 159:1 241:14 326:20</p> <p>fatal ^[2] 285:2,5</p> <p>fate ^[2] 356:21 357:3</p> <p>father ^[1] 17:20</p> <p>fatigue ^[3] 118:1 268:14 293:17</p> <p>Fatty ^[1] 62:11</p> <p>favor ^[1] 242:8</p> <p>favorable ^[5] 13:2 134:16 355:6 374:9 383:15</p> <p>favorites ^[1] 18:5</p> <p>FDA ^[78] 2:21 3:26 4:13 5:15,16,17 7:2 9:11,21 11:19 12:1 15:6,17 19:16 20:8 21:20 25:20 28:11 29:7,15 33:22 41:9 96:18 101:13 102:11 108:21 109:16 111:10,13 112:1 114:10 115:7 116:7 124:3 126:9 127:1 128:7 130:13,14 132:11 135:10 141:16 146:9 147:20 150:16 157:13 185:10,15,17 219:12,13,15 222:6,16,20 223:1,10 224:5 231:1 242:14 246:2,9 250:20 251:7 252:5 301:5 308:21 309:13,15 310:7,11 311:13,19 312:1 320:1 368:3 372:3 385:17</p> <p>FDA's ^[5] 15:19 53:13 114:3 318:21 327:15</p> <p>FDA-approved ^[2] 71:17 73:17</p> <p>feasible ^[1] 29:18</p> <p>feature ^[1] 105:17</p> <p>features ^[2] 31:6 36:4</p> <p>February ^[2] 14:6 45:7</p> <p>fed ^[3] 63:20 65:21 326:3</p> <p>Federal ^[1] 119:10</p> <p>feed ^[1] 360:4</p>
---	---	--	---

F

F ^[1] 222:1

face ^[4] 18:13 30:3 163:16 376:11

fact ^[28] 18:1 70:4 107:20 156:6 175:14 182:18 201:10 203:5 220:17 229:16 232:17 234:6 265:19 270:5 292:16 304:22 305:12 309:10,12 310:14 328:9 347:21 353:14 360:18 361:8,13,18 376:14

factor ^[5] 47:5 78:10 160:13 287:17 341:16

factored ^[1] 313:20

factors ^[8] 72:8 91:18 160:12

<p>feedback ^[2] 152:13 252:1</p> <p>feel ^[8] 22:18 115:9 178:16 239:6 331:13 334:20 354:16 377:4</p> <p>feeling ^[5] 24:22 150:1 154: 21 313:7 368:22</p> <p>fell ^[1] 305:2</p> <p>fellow ^[1] 233:4</p> <p>felt ^[11] 116:21 125:3,10 131: 8,14 132:3 133:15,16 167:8 271:8 281:13</p> <p>female ^[3] 209:17 231:13 266: 4</p> <p>females ^[3] 77:17 255:8 278: 22</p> <p>fen-fen ^[4] 236:15 237:4,5 242:16</p> <p>fence ^[1] 373:15</p> <p>fetal ^[1] 231:17</p> <p>fetuses, ^[1] 231:4</p> <p>few ^[20] 59:12 63:8 100:13 106:7 128:1 141:15 142:15 167:6,8 172:19 173:7 240:14 241:21 258:11 259:17 262: 16 320:15 346:2 352:9 356:7</p> <p>fewer ^[2] 25:12 106:12</p> <p>field ^[4] 16:10 49:7 52:8 382: 21</p> <p>Fifteen ^[1] 125:13</p> <p>fight ^[1] 24:19</p> <p>figure ^[4] 178:2 237:16 315: 16 360:21</p> <p>figured ^[1] 238:11</p> <p>figures ^[4] 94:7 122:13 177: 11 346:13</p> <p>file ^[1] 46:5</p> <p>fill ^[1] 143:8</p> <p>final ^[3] 12:1 254:11 325:21</p> <p>finally ^[18] 33:1 35:4 43:5 50: 4 62:1 69:14 70:20 86:14 91: 13 101:9 103:1 136:16 139:5 159:12 165:10 169:3 242:21 367:6</p> <p>financial ^[10] 8:20 9:21 10:5 118:2 223:4,7,13,14 224:7 243:13</p> <p>find ^[11] 65:2 183:2 292:13 301:21 316:1 331:4 333:10, 11 374:20 375:10 379:6</p> <p>finding ^[7] 83:1 85:5 88:20 236:10 266:18 272:17 354: 15</p> <p>findings ^[11] 25:4,5 26:7,18 186:8 200:13 211:5 218:2 227:15 229:20 251:17</p> <p>fine ^[1] 167:8</p> <p>fine-tune ^[1] 51:10</p> <p>finish ^[2] 138:9 303:20</p> <p>finished ^[1] 309:21</p> <p>fire ^[1] 24:3</p> <p>firm ^[1] 10:6</p> <p>firmer ^[1] 306:20</p> <p>firmly ^[1] 151:6</p> <p>firms ^[1] 9:20</p> <p>first ^[76] 5:9 10:16,22 12:11 17:17 20:18 23:21 28:6 29: 11 36:13 49:20 51:16 69:12</p>	<p>70:11 74:19 77:9 89:14 96: 14 97:3 98:3 110:18 115:1, 10 135:12 140:8,21 142:17 146:17 148:8 154:8 156:12 157:3 158:17 160:17 170:17 175:9 176:1 182:11 186:2 190:7 198:2 214:10 222:2 223:18,19 231:21 232:9 235: 20 237:11 251:16 253:19,22 258:5 260:8 262:6 263:3 284: 10,14 285:16 286:10 294:7 300:3 301:10 317:1,10 329:1, 16 330:11,18 336:2,12 340: 10 352:2 353:8 362:20 374: 11</p> <p>first-line ^[1] 73:7</p> <p>fit ^[1] 161:2</p> <p>five ^[5] 29:20 131:13 268:7 283:15 307:9</p> <p>five-year ^[1] 365:5</p> <p>fix ^[2] 29:2 30:10</p> <p>fixed ^[2] 260:6 285:12</p> <p>fixed-effects ^[1] 260:3</p> <p>flag ^[1] 20:13</p> <p>flattens ^[1] 330:19</p> <p>flavor ^[1] 263:19</p> <p>flaws ^[2] 368:20,21</p> <p>fleeting ^[2] 35:8,20</p> <p>Flegal ^[5] 2:7 7:20,20 362:4,4</p> <p>Flegler ^[2] 384:13,14</p> <p>floor ^[2] 346:22 372:21</p> <p>Florida ^[1] 7:17</p> <p>flow ^[2] 58:22 59:3</p> <p>fluctuations ^[1] 360:16</p> <p>fly ^[1] 143:18</p> <p>fMRI ^[1] 59:1</p> <p>focal ^[1] 319:13</p> <p>focus ^[19] 11:2 93:17 94:3 95: 8 135:5,6 140:8 141:11 185: 21 186:5 187:13 189:11 190: 6 200:13 207:6 251:18,19 317:11 378:6</p> <p>focused ^[7] 186:8 256:14 257:15,19 276:11 294:14 358:17</p> <p>focusing ^[2] 97:22 102:17</p> <p>fold ^[2] 120:12 314:22</p> <p>folks ^[3] 294:5 355:9,10</p> <p>follow ^[12] 94:3 254:4,14 265: 20 268:19 347:1 351:4,5 378: 15 379:11,13 380:12</p> <p>follow-up ^[3] 155:21 163:7 175:18</p> <p>followed ^[11] 37:13,18,21 38: 19 39:3 50:14 66:6 95:1 185: 10 186:4 204:19</p> <p>following ^[24] 8:15 11:14,21 18:9 24:19 44:4 45:8 46:10 51:3 91:18 108:16 148:8 151: 9 157:15 173:1 188:11 199: 20 205:17 209:18 211:7 244: 1 252:8 274:14 299:21</p> <p>follows ^[2] 12:22 230:14</p> <p>FOOD ^[17] 1:2 36:19 61:10 63: 6,19 64:4 67:6,13 68:9 174:4, 5,6,9 186:21 189:18 200:10 326:4</p>	<p>foods ^[1] 190:2</p> <p>football ^[1] 380:21</p> <p>footnote ^[1] 312:5</p> <p>FOR ^[522] 1:3 5:10,15 7:21 8: 19 9:21 10:2,16,19 11:10,12 12:2,6 13:3,14,15 14:8,15 16: 3 20:2,15,21 21:4,20,20 22:8 23:16 24:1,18 26:1,11 27:6 28:2 29:7 30:4 31:10 32:16 33:18 34:9 35:8 36:22 37:2 38:4,4,18 39:1,22 41:7 42:8 44:11,18,20 45:4 46:1,4,5 47: 9 48:1,10 49:8 50:2,5 52:20 53:1,2,10,15,21 54:11,19 55: 10,16 56:18 57:17,22 60:1 61:7 62:2,9 63:1 64:7,15 65: 7,11 66:6 68:16 70:8 71:5,7, 14,16,17 72:2 73:3,18,22 74: 16,21 75:11 79:6,13,17 80:11, 18 81:9,18,20,20 82:14 84:19, 21 86:14 87:7,20,20 90:12,13, 14,16 92:22 93:3,4,14,22 95: 5,10,13,14,20,21 96:5,12,12 97:22 99:2,5 100:17 102:8 104:13 105:6 107:1,3,11,21, 21 108:1 109:6,8 111:4,5,11, 14,15,22 112:1,3,12,16,16,22 113:14,15,20 114:22 115:6,9, 21,22 116:3,15,21 117:6,19 119:14 120:3,20 124:7,8 125: 6,17,21 126:14 128:12,14 129:14,15,20,20 130:5 131: 19,19 134:5 135:15 136:15, 17 137:4,6,11 138:18 139:14 140:16 141:9,22 142:3,3,10 143:2,11 145:3,21 147:4,12 148:4,16 149:9,10 151:3,8,8, 16 152:3,11 153:5,10,17 154: 18 156:14,18 157:7 159:2,13, 18 160:9,21 161:22 162:5,11, 14 163:5 164:9,22 168:1,5,9, 19,21,22 169:21 170:1,4 172: 20 174:4 175:5,16,18,21 177: 20 178:5 180:8 182:21 183: 14,20,20,20 184:16 185:7 190:3,4,17 197:12,17 198:3 199:1,4 202:19 203:9 205:5, 9,12,15 207:19 208:1 214:11, 17 215:16 216:22 217:7,18 219:15 221:5 222:17 223:1,7, 20 224:17 225:15 227:2,8,16, 17 228:13 229:9,10 232:19 233:3,4,16 236:21 237:8 240: 1,7,12,14 241:17,21 242:21 243:3,17 245:2,5,22 246:2,11, 11,13 247:20 248:8,19 249:9 250:11,17 252:5,6,20,20 253: 14 254:17 255:1,16 256:13, 21,22 257:12,14,16 258:12, 19,21 260:1,4 261:18 263:3, 19 266:17 268:3 269:4 270:9, 13,18 272:3,4,5 273:11 274: 14 276:6 277:17,17 278:22 280:11,17 281:14 282:19 283:13 284:12 285:20,21 288:7,15 289:14 290:8,12,14 292:20 293:4,21 294:8,13,22</p>	<p>295:4,12,17 296:13,19 298:8 299:5,8,18,22 300:3,3,7,20 301:2 302:8 303:3,8,9 304:3 305:14 307:6,8,16 308:10,22 309:4 310:4,8,13,13,19 311:1, 2,9 312:6 313:12 314:16,17, 21,22 316:1,15 320:6,12 322: 8,9 323:7,20 324:6,10 325:15 326:2,15,16,21 328:6,11,12, 19,21 332:8 333:9 334:4,11, 14 335:11,15 336:3,20 337:1 338:18 339:4,7,12 340:11 341:2,14,22 342:14 343:7,14, 14,16 344:7,15,16 345:11,20, 22 346:7,10,10,13,17 347:11 351:19 352:4,19 353:1 356:5, 6,7,11 357:8 359:10 361:4,12, 22 362:21,21 363:1,19 364: 20 367:3,16 369:7,8 370:1 371:6,6 372:10 373:14 375:3, 15,22 377:8 381:9 382:13 383:7,7,11,14,16</p> <p>forebrain ^[1] 61:10</p> <p>forebrains ^[1] 67:7</p> <p>forefront ^[1] 242:20</p> <p>forego ^[1] 166:7</p> <p>forest ^[2] 264:12 265:9</p> <p>forever ^[2] 365:10,12</p> <p>forget ^[1] 286:4</p> <p>forgot ^[1] 383:6</p> <p>form ^[10] 23:14 74:1 103:19 104:3 143:8 149:4,5,20 266: 16,19</p> <p>formal ^[2] 123:2 282:21</p> <p>formed ^[1] 270:8</p> <p>forming ^[3] 195:8,10,10</p> <p>forms ^[9] 143:2 258:20 280:3 281:16 282:15 290:21 303: 11 319:6 382:17</p> <p>forth ^[1] 130:4 225:5</p> <p>fortuitously ^[1] 24:3</p> <p>Forty-eight ^[1] 129:11</p> <p>Forty-five ^[1] 118:8</p> <p>forward ^[9] 14:10 121:7 172: 19 173:16 238:5 254:22 359: 8 385:13,16</p> <p>found ^[15] 25:8,9 52:4 63:10 119:7,8 218:7 219:19,20 228: 14 234:4 236:9 302:1 308:9 318:9</p> <p>four ^[26] 13:21 32:2 39:7 49: 20 65:18 83:16,17,19,21 128: 4 133:14 151:22 156:10 158: 16 174:13 175:12 177:12 228:4 229:18 230:6 253:22 271:1 284:22 286:13 312:4 336:18</p> <p>Fourteen ^[1] 131:12</p> <p>fraction ^[1] 334:12</p> <p>fragment ^[2] 137:14 138:3</p> <p>frame ^[2] 57:2 135:9</p> <p>FRANCO ^[1] 376:10</p> <p>frankly ^[3] 241:6,16 242:8</p> <p>FRCP ^[1] 2:13</p> <p>frequency ^[7] 31:6 35:12 36: 4 124:10 269:13 340:22 343: 4</p>
---	--	--	--

<p>frequent ^[9] 78:11 83:1 105:16 113:3 123:9 124:9 136:11 175:22 363:18</p> <p>frequently ^[16] 70:16 79:3 107:14 115:12 122:20 124:15 152:21 206:22 262:10 263:8 264:3 273:7,10 302:19 341:18 347:22</p> <p>from ^[222] 3:25,29 5:17 7:20 9:16 10:1 11:15,18 14:21 15:18 17:16 18:6 21:21 23:13 24:12 30:18 36:8,14 37:15 39:19 40:5,7,9,16,18,19 41:17 42:5 45:8,15,16,18,21 52:8 54:4 62:11,19 64:8 70:17,21 72:1,18 73:8,9,11 74:11,11 77:21 81:9 83:18 88:14 89:4 93:22 94:4,18 95:2 96:6,17 102:1,10 103:4,20 108:1,9,14 109:5 110:15 111:10 114:10 115:14 116:16 119:7,15 122:13 128:4 136:20 137:12 143:21 145:9 155:7 156:9 159:7 166:4 169:3,6 170:11,14 172:2,15 176:7 177:17 182:8,10,20 184:15 185:15 193:5 196:22 198:6,9 202:19 209:10 210:5 212:5 215:15 217:19 220:6,22 221:1,2 222:6,8,9,11 223:16 227:8 228:20 230:22 234:22 235:9,13 238:19 240:10 243:14,14 250:10 251:14 252:1 254:1,14 255:21 256:6 257:5 258:17 259:9,11 260:8,11,20 261:19 266:6,9 267:2,5,16,21 268:20 269:21 270:13,18 273:11 274:13 275:3 276:5 280:4,17,20 282:1,6,22 284:10 290:4,16 291:10 293:12,22 294:19 296:10 301:6 302:11 304:16 307:12 308:8 309:2,14 310:1 311:14,15,19 312:2,3,11 313:11 317:9,15 318:4 319:20 325:6 328:5 331:14 338:5,6,17,20 345:5 347:15,21 348:4 349:5,18,22 356:22 357:7 358:20 360:9,19 364:4,4 368:2,3 369:3 372:12 375:8,8 377:2,6 378:5 380:8 381:10,14 382:11</p> <p>front ^[1] 119:9</p> <p>frontal ^[1] 341:13</p> <p>frustrating ^[1] 301:4</p> <p>Frustration ^[1] 71:13</p> <p>full ^[9] 5:7,7 10:14 72:20 143:15 173:8 197:3 250:19 309:16</p> <p>fully ^[13] 37:10 41:14 89:7,18 90:5 92:12 102:16 148:22 155:9 234:14,19 260:18 370:15</p> <p>function ^[15] 66:19 90:22 91:7 178:21 187:3 189:5,18 191:19 192:17 195:1 201:10 261:4 292:10 295:16 366:4</p> <p>functional ^[1] 65:3</p>	<p>functionality ^[1] 244:18</p> <p>functioning ^[6] 178:4,6,6,7,8 357:22</p> <p>functions ^[16] 186:17,20 187:1,8,16 189:9 191:2 194:8 195:21 199:14,17 200:1,20 203:18 214:18 225:13</p> <p>fundamental ^[2] 331:11,15</p> <p>funded ^[1] 15:16</p> <p>funding ^[1] 235:13</p> <p>further ^[19] 14:10 79:17 112:10 118:11 138:1 139:22 150:8 185:12 205:8 258:16 269:4 288:19 298:1 302:2 307:2 340:15 355:3 368:15 385:19</p> <p>Furthermore ^[4] 26:13 183:16 267:5 275:3</p> <p>future ^[14] 27:22 29:16 95:19 107:4 121:2 136:9 139:2 236:19 244:19 317:14 357:5 367:7 372:14 385:18</p> <hr/> <p style="text-align: center;">G</p> <hr/> <p>G ^[5] 2:23,26 3:8 5:1 222:1</p> <p>G-protein ^[2] 54:17 56:13</p> <p>G-protein-coupled ^[1] 188:21</p> <p>G-proteins ^[4] 193:10 196:1,8,9</p> <p>GABA ^[3] 194:16 197:12 210:20</p> <p>GABAergic ^[1] 193:17</p> <p>gain ^[7] 61:11 91:22 158:22 163:21 314:5 363:20 379:2</p> <p>gained ^[3] 169:3 321:21 359:13</p> <p>gaining ^[2] 359:12,15</p> <p>gait ^[3] 127:20 128:1,5</p> <p>gallbladder ^[1] 160:3</p> <p>ganglia ^[4] 51:20 190:17 225:4 261:3</p> <p>gas ^[2] 20:11,16</p> <p>gastric ^[1] 163:5</p> <p>gastrointestinal ^[3] 20:17 162:1 328:12</p> <p>gather ^[2] 149:2 321:14</p> <p>gathered ^[1] 149:15</p> <p>gathering ^[1] 222:17</p> <p>gave ^[1] 261:15</p> <p>GBMS ^[1] 56:12</p> <p>gender ^[9] 77:18 86:9 278:12,21 300:15,19,20 307:17 310:4</p> <p>gene ^[1] 195:22</p> <p>general ^[14] 9:6 35:9 107:5 137:4 179:3,19 204:11 217:9 228:13 280:15 298:11 313:7 349:5 369:14</p> <p>generalizability ^[1] 255:6</p> <p>generalization ^[2] 356:18 382:13</p> <p>generalize ^[1] 233:15</p> <p>generally ^[15] 35:13 78:20 107:11 193:7 197:9 202:6 204:9 205:22 212:1,20 218:4 287:18 309:5 319:20 335:2</p> <p>generate ^[1] 197:7</p> <p>generated ^[1] 195:15</p>	<p>generating ^[1] 214:3</p> <p>generation ^[2] 190:4 382:1</p> <p>generic ^[2] 153:14 178:19</p> <p>generous ^[1] 370:4</p> <p>genetic ^[1] 244:4</p> <p>genotoxicity ^[2] 204:20 231:11</p> <p>gentleman ^[3] 286:20 287:3,12</p> <p>gentlemen ^[2] 49:15 93:10</p> <p>geographical ^[1] 278:12</p> <p>Georgetown ^[1] 262:2</p> <p>Germany ^[2] 293:13 376:16</p> <p>gesture ^[1] 16:21</p> <p>get ^[50] 23:17 29:7 30:13 33:2 35:1,17 36:3 56:14 65:22 121:8 130:11 133:6,7,18,19 146:15 162:14 181:11 185:13 228:20 230:2 237:5,6,17 239:10,12 294:9 305:7 307:9 308:9,10 312:7 317:14 324:17 339:11 346:13 351:3,3,4 361:17 370:20 373:6 374:20 375:5,7 377:22,22 378:1,22 382:18</p> <p>gets ^[4] 209:12 237:15 302:10 382:1</p> <p>getting ^[16] 34:6,7 174:16 185:2 227:1 236:4,5,12 306:13,20 324:17 328:2 333:14,17 350:2 361:15</p> <p>GI ^[9] 98:18,19 100:7 126:5 135:5 189:15 201:1 225:7 377:18</p> <p>Gill ^[1] 49:5</p> <p>Gilman ^[32] 2:13 6:22,22 170:13,15 171:12 172:10 173:17 174:2,11 176:10 300:21 301:1 303:22 305:16 307:4 317:10 318:19 319:15 340:5,7 342:16,20 371:16 374:11,12,15,15 379:22 380:1 383:21,22</p> <p>give ^[20] 10:10 11:19 15:10 30:7 32:14 34:2,2,16 49:16 142:14 144:14 153:4 172:13 185:1 223:19 228:4 246:20 315:3 327:9 329:18</p> <p>given ^[40] 21:16 34:16 75:11 89:15 90:1,2 93:21 104:18 105:14,22 126:16,20 137:13 142:7,8 153:12 164:6 169:21 226:6,20,21 228:14 232:17 236:17 241:10 253:16 265:19 268:10 272:16,18 292:8 293:5,19 326:18 332:8,22 335:10 337:19 349:20 368:18</p> <p>gives ^[7] 30:9 40:21 41:19 263:19 330:15,15 358:8</p> <p>giving ^[6] 33:20 57:14 239:15 316:4 321:15 381:1</p> <p>glad ^[3] 241:7 329:17 335:12</p> <p>gland ^[1] 225:7</p> <p>glaring ^[1] 358:5</p> <p>GlaxoSmithKline ^[1] 9:18</p> <p>glial ^[1] 194:2</p>	<p>glitazone ^[1] 87:7</p> <p>global ^[3] 39:8 56:13 58:20</p> <p>glucose ^[9] 66:18 67:18 72:22 87:4 88:4,6 92:1,20 164:19</p> <p>glutamate ^[5] 50:21 58:8,9 193:3 194:17</p> <p>glutamatergic ^[1] 193:16</p> <p>glycemic ^[3] 85:15 87:10 88:10</p> <p>go ^[46] 5:10 16:4 23:6,10 34:15 105:3 108:8,18 109:19 133:1 153:20 165:8 177:1 180:11,14 181:21 195:17 209:6,10 222:5 225:1 236:8 294:7 301:4 305:16 310:14 316:18 324:3 325:22 329:9 333:21 336:1,4 338:3,14 352:20 353:19 354:15 357:10 359:19 372:4 375:19 379:1,7,18 383:5</p> <p>goal ^[2] 154:20 298:19</p> <p>goals ^[2] 71:6 72:2</p> <p>God ^[1] 18:13</p> <p>goes ^[9] 18:17 64:3 160:6,8 302:11 323:4 353:2 359:7 382:20</p> <p>going ^[80] 5:8,9 10:9,21 13:17 15:16 16:4 23:10 25:11 35:17 36:10,11 105:12 121:7 141:13 147:10 148:9 149:17,19 155:16 156:4 174:19 185:3,5 222:12 225:9 229:1 237:21 238:1 239:17 240:10,13,14 241:4 246:19 265:22 293:20,21 294:9 304:10 310:18 315:12 317:14 319:10 323:15 324:4 325:22 328:2,18,22 332:21 333:7,16,19,21 337:2 338:12 339:7 347:18 354:19 355:17 357:17 361:11 363:12 364:18,21 367:19 370:12,22 371:1 372:8,13 373:2 374:9 377:5 378:19 381:15 382:7,22 383:5</p> <p>goldmine ^[1] 379:21</p> <p>gone ^[2] 379:14 385:11</p> <p>Good ^[34] 5:3 15:7 33:21 35:11 36:6,18 42:17 49:14 69:8 81:22 93:9 156:11 236:11 237:12 239:6,6 243:10 251:9 319:22 323:9,21 329:20,22 330:2,8 332:16 335:13 351:5 353:4 364:11 367:17 368:22 370:21 373:6</p> <p>Goodman ^[21] 2:14 7:16,16 177:19,20 180:4 219:10,11 343:20,21 344:17 346:21 347:1 356:4,4 358:12,15 373:13 376:11 384:9,10</p> <p>got ^[11] 30:21,21 128:16 247:13,13,14 248:2 311:21 352:8 353:10 365:12</p> <p>gotten ^[3] 350:3 359:17 383:10</p> <p>Gould ^[1] 16:2</p> <p>GPR ^[1] 53:3</p>
--	---	--	---

<p>GPR55 ^[1] 59:13 graciously ^[1] 222:12 graded ^[1] 55:8 gradually ^[1] 155:5 grand ^[2] 130:3 319:14 graph ^[1] 326:11 graphically ^[1] 197:2 graphs ^[1] 171:14 grasp ^[1] 306:13 great ^[12] 14:7 187:2 189:21 203:5 242:5 304:2 306:12 324:14 332:10 333:21 352: 18 362:2 greater ^[26] 13:5,6 38:14 40:8 47:4,6 53:15 56:15 91:9 94: 15 95:3 99:15 102:7 106:1 178:9 212:1 228:22 252:9,14 255:13,18,22 308:15 355:15 361:5 383:18 greatest ^[2] 75:16 330:2 grossly ^[1] 342:6 ground ^[2] 326:20 354:5 grounds ^[1] 273:11 Group ^[73] 4:5 50:13 63:20 66:15 75:10 79:12,13 86:21 89:16,20,20,22 95:20 103:9 105:1,2,16 109:11 115:11,12, 13,21 116:4,6 120:10 125:1 126:3 170:4 178:10 224:2 227:9,10 255:11 259:10 275: 18 276:10,11 277:2,16 278: 14 279:14 281:5 282:22 283: 13 284:12,14 285:14,15,15 300:12 302:14 308:16 318:4 321:14 323:5 327:13,13,15 332:11 333:3,11 341:17,19, 19 343:7 344:4,5 355:8,14 356:10 359:1 364:19 377:22 Group's ^[1] 378:3 grouped ^[2] 110:1 262:3 grouping ^[1] 95:20 groupings ^[1] 109:20 groups ^[15] 33:22 65:18 85: 16 98:22 99:4 104:9 107:17 157:13 178:9 228:18 229:2 259:16 289:14,18 368:11 growing ^[3] 74:4 139:3 157: 16 guess ^[6] 173:9 293:11 300: 13 337:13 358:9 373:13 Guest ^[5] 3:9 9:12 13:14 14: 20 15:3 guidance ^[13] 38:3,12,17 39: 10 252:5,16 308:21 309:13 339:2,11,12,14 369:18 guide ^[6] 141:15 142:6 150: 14,14 153:11 158:6 guidelines ^[9] 19:18 73:3,6, 12 81:20 95:2,5 160:9 356: 10 gun ^[2] 24:2,3 Gunshot ^[1] 119:1 Gural ^[28] 3:13,22 36:14,18, 21 49:12 68:22 93:1,8 94:8 97:20 139:15 140:2 157:19 170:7,9 171:6 175:2 180:17 311:2,16 312:3 320:4 338:16</p>	<p>345:6,18 346:20 347:11 gut ^[3] 52:5 67:9,12 guy ^[1] 24:2 guys ^[1] 175:1</p> <hr/> <p style="text-align: center;">H</p> <hr/> <p>H ^[1] 2:22 had ^[106] 9:15 15:17 19:17 21: 16 22:8 25:20 26:14 27:18 39:2,13 46:9,19 66:14 77:4,7 79:6 96:6,20 102:14 103:19 104:13 105:4,5 106:14,19 109:1 110:2,20 113:13,15 117:19,19,21 118:9 119:8 126:18 127:22 128:17,18,20 130:8 132:5 135:21 139:1,20 144:19,20 154:9 163:7,8 167: 7 175:13 181:18,22 222:11 224:15 228:6,22 229:9 232:8 235:3 238:1 240:4,21 253:12 257:5 258:21 259:18 267:22 268:3,6 271:11,12 275:13 279:21 282:7,16 287:3,12 294:13 296:13 302:17 305: 13 306:12 310:17 311:19 313:22 315:12 318:2 319:3,4, 20 325:8 326:3 334:2 336:15 339:20 341:8 356:21 357:11 358:3 359:16 367:2 369:15 376:4 385:4 half ^[8] 12:6 113:13 124:13 250:18 254:12 296:6 332:22 363:14 half-hour ^[1] 34:17 half-life ^[3] 42:21 258:1 361: 16 hallmarks ^[2] 42:12,16 haloperidol ^[1] 283:16 Hamilton ^[1] 28:10 hand ^[4] 325:4 357:15,20 359: 14 handling ^[3] 114:18 115:13 334:11 handout ^[1] 170:19 handouts ^[1] 250:16 hands ^[2] 152:12 329:8 hang ^[2] 17:19 20:11 happen ^[6] 217:7 232:4 238: 10 333:19 337:2 361:12 happened ^[2] 20:7 375:11 happening ^[3] 156:11 330:20 331:9 happens ^[8] 16:16 17:6 173: 1,20 330:16,22 332:12 351:2 happy ^[2] 333:16 377:4 hard ^[12] 104:18 130:2 173:22 220:3 237:5 349:7,9 356:15 357:8 359:18 372:4 381:15 harm ^[12] 24:1 25:18 237:9 343:14,17 344:8,15 345:10 346:7 347:4,8 364:6 Harmonization ^[2] 95:3,4 harms ^[1] 347:9 has ^[129] 6:4 8:12 9:11,15,21 11:14 13:2 14:4,6 18:11 24: 17 27:11 35:2 37:6 38:2,19 42:2,13,17,19 48:21 49:6 53: 1,9,14 54:14,16 59:3 61:7,12</p>	<p>72:5,12 87:9 88:10 91:1 94: 16 111:20 112:7 113:10 119: 15 120:14 122:14 127:1,5,18 128:7,17,18 134:18 136:5 137:19 138:13 139:9,12 145: 12 149:21 150:3 158:3 165: 18,21 168:16 169:18 183:17, 22 184:14 190:2 196:13,16 197:11 198:11 203:17 215:6 219:6 224:10 227:18,22 228: 14 233:5,12 234:11 236:8 237:12 239:19 242:14,14 243:13 245:14,16 255:2 269: 11 274:2 280:10 286:7 287: 19 296:14,16,18 301:8 303: 12 304:1 309:18 312:9 327:6 329:20 331:6 332:7,7 333:14 337:9 343:5 346:15 348:9 349:17 351:12 352:10 353: 14 354:4 357:18 360:17 364: 17 365:17 372:1 373:3,22 375:8 376:4 380:17 383:15 385:11 hasn't ^[1] 174:22 hats ^[1] 337:5 have ^[470] 5:7,13 8:10,22 10:9, 14 11:21,22 12:5 15:20 16: 13 17:7,7,8 18:9,14 19:5,20 21:7 22:8,10,11,13,14,16,21 23:8,22 24:7,9 27:17,18 28:7, 17,21 30:18 31:6,19 32:2 33: 11,18 34:16 35:11 38:14 39: 11,12 40:15,17 41:14 42:2 44:12,20 46:19 47:18 48:3,7, 9 54:20 55:5,19,20 56:4 57: 10,18 59:17 60:5 62:2 63:5 66:2 67:2 68:11,18 81:2,22 87:16 94:9,17,18 100:16 103: 15 104:19 106:19 108:18 117:7 120:4 121:8,12 127:10 129:1 130:22 132:4,15,18 133:1,10 134:3,9,10,12,21 137:1,3,14,17 139:20 140:9 141:1 143:1,14,15,16,19 144: 2 145:13 146:7 147:15 148:6, 22 149:4,22,22 150:4,21 152: 8,12 153:20 154:9 155:14,21 156:6,7,10,16 157:9 158:19 161:13,15 162:8 164:3,4 165: 13,16 166:1,20 167:4,10 170: 15 171:5 172:22 173:8,12,22 174:1,7 175:10,20 176:6 177: 6 179:13,16 180:4,8 181:18 182:16 184:1,4,14,16,17 185: 6,19 187:2,5,18 189:1,5,20 190:15,19 191:21 194:8,21 196:6,9,19 197:10,22 198:13, 17,20 203:4 207:11 211:19 216:1,4,8,12 218:14 219:21 220:5 222:4,7,11,15 223:5,12, 17,17 224:7,13,15 225:1 226: 2,13 227:19 228:15 229:1 230:5,16 231:19 232:3,4,15, 20,21,21 233:8,19 235:1,1,17 236:3,5 237:3,7,20 238:2,3,5 239:4,21 240:4,9,13,18 241:7, 16,18 245:5,9 246:7,19 249:8</p>	<p>251:3,4 256:21,22 257:2,5,15 260:17 262:19,20 265:3,20 267:13 269:20 271:3 272:10 274:11 277:12 279:15 280:1, 7,11 285:14 286:5,13,17 291: 18 292:16 293:13,22 295:4,5, 5 296:15,17,19 297:2 298:12 299:21 301:1,7,21 302:5 303: 3,7,10 304:11,18 306:2,7,15, 16,18,19 307:1,11,19 308:7 310:6,12,17,21 311:15,21 313:13,13 314:3,11,13,15,17, 18 315:4 317:20 318:12,17 319:5,6,12,13,17,20 320:2,4, 8,15,16 321:4 322:5,6,7,10, 21 324:7,19 325:3,21 327:2 328:10 329:17 330:1,10,11 331:8,17 333:22,22 334:5 335:11,18 336:12,12,22 337: 2 338:12,13 339:6,7,8 341:8, 10,12,20,22 342:3,3 343:9 344:3,22 345:12,14 346:21 347:17 348:21 349:9 350:3,5, 6,20,22 351:15 352:1,3,7,21 353:10,11,15 354:9,10,18,22 355:13 356:17 358:10,17 359:12,13,14,17 360:2 361:1, 22 362:8,14 363:12,20 364: 14,18,19 365:2,5 366:11 367: 10 368:19,22 369:11,15,17, 19,22 370:4,16 371:5,13 372: 2,3,3,8,9,19 373:1,9,12 374: 16 375:2,18 376:8,14,15,20 377:14,15,21 378:6 379:1,7, 10,13,18 380:18 382:2 383:2, 6 384:22 385:3,12 haven't ^[8] 41:2 174:11 195:5 241:14 297:19 313:20 345: 13,13 having ^[20] 26:11 27:22 46: 12 138:22 139:1 145:10 172: 5 180:13,14 189:6 196:17 220:1 234:6 279:17 280:10 330:11 352:14 369:4 377:4 383:10 Hayes ^[2] 380:20,21 HbA1C ^[1] 164:19 HDL ^[13] 67:17 78:13 82:22 83:5,16 90:2,9,12,12 92:5 164:20 253:9 297:7 he ^[19] 18:6 25:1 103:3 118:9, 13,14 119:11 127:5 155:18 201:21 223:18 287:4,6 293: 21 324:12 374:18 380:21,22 385:1 head ^[3] 8:4 93:13 327:14 head-to-head ^[1] 382:14 headache ^[1] 27:17 headaches ^[1] 167:2 headed ^[1] 331:2 HEALTH ^[31] 1:1 4:5 7:15 69: 19 101:14 141:5,9 142:10 143:22 145:1 146:4 149:12 152:1 159:9 165:1,2,16 166: 12 168:4,20 178:7 179:3,7 224:1 244:14,22 245:12,19 298:16 362:21 363:1</p>
--	---	---	--

health-care ^[1] 335:1 healthcare ^[1] 245:13 healthy ^[1] 206:14 hear ^[18] 27:19 40:13 42:4 46:1,21,22 47:10 65:8 200:13 212:15 241:3 312:14 321:12 330:7 343:22 344:19 369:10 383:4 heard ^[32] 18:10 45:21 86:2 88:14 108:13,18 137:10 140:9 158:7 164:3 187:2,18 189:21 196:19 197:8 198:13 203:5 224:13 225:1 226:2,13 229:1 234:22 235:17 238:13 240:9 269:20 327:22 330:1 333:22 373:1 376:21 Hearing ^[11] 4:2 8:11 11:22 185:9,9 221:6 222:14,19 223:2 369:15 374:3 heart ^[6] 139:1 159:18,19 160:2 183:3 244:9 heavier ^[2] 176:17 361:14 height ^[1] 154:11 help ^[15] 15:19 31:21 35:17,19 52:5 102:4 151:2 243:4 246:8 319:9 331:22 334:15 370:5 375:1 380:22 helpful ^[5] 35:7 308:19 314:9 369:17 370:9 helping ^[1] 316:8 helps ^[1] 35:4 hemoglobin ^[2] 253:9 297:7 Hence ^[1] 366:7 Henderson ^[7] 2:8 7:22,22 364:13,13 384:15,16 hepatocytes ^[1] 194:1 Her ^[9] 11:10 24:19,20 109:14 121:6 135:21 250:18 268:4,7 Herb ^[1] 218:18 herbal ^[2] 71:16 161:13 here ^[130] 10:19 13:15 15:10 21:1 23:3 29:13 32:21 37:3 38:16 40:4 41:5,13,15 43:17 46:12,17 52:22 53:12 54:2,6,21 56:21 57:5 58:5,15 59:6,13 62:12,14,18 63:1,13 65:19 66:4,8 72:17 75:5,17 78:22 79:4 80:6 81:11 82:18 83:2,6,14,22 85:22 86:19 87:17 88:17 93:11 94:8 95:15 97:11,12 98:14 99:5 103:10 104:21 106:8,9,12 109:20 111:3,4 112:20 113:7 114:13 119:1 120:5,7,9 124:7,21 125:7 127:6,8 128:9 131:17 132:17 133:3 143:18 150:4 151:20 154:2 156:4,20 159:22 160:7,16 166:18 167:18 171:14 173:8 175:12,17 177:13 210:7 228:4 232:21 247:19 248:12,19,20,21 262:20 266:1 278:3 281:3 286:3 291:9 294:22 302:1 311:11,12 312:4 313:17 316:3 319:1,22 320:9 329:19 336:22 338:16 350:4 369:21 377:15 380:2,17 herself ^[1] 375:10	hesitancy ^[1] 34:20 hesitate ^[1] 314:18 heterozygous ^[1] 66:2 hetromeric ^[1] 195:11 Hi ^[2] 352:1 364:13 hierarchy ^[1] 123:5 high ^[36] 53:1 56:4,14 63:21 77:22 78:4,6,12,13 103:9 159:3 171:15,16 209:19 229:22 230:8 253:20 254:5,13 261:2 315:14 340:9,11,12,13 349:20 359:6,15,20 361:1,22 362:9 363:16,16 364:14 366:18 high-affinity ^[1] 52:17 high-level ^[5] 276:10,11 277:16 302:13,14 high-risk ^[1] 272:20 higher ^[27] 82:4 86:10 111:1 115:5 124:9 165:22 191:2 205:19 210:18 213:22 227:19 228:15 265:3,16 275:17 277:17 278:14,22 290:13 293:6 308:6 310:14 314:22 344:4 350:21 355:9 356:19 highest ^[3] 138:21,21 208:8 highlight ^[4] 81:13 261:22 262:16 298:17 highlighted ^[3] 260:13 287:3 377:19 highlighting ^[1] 106:9 highlights ^[2] 264:1 266:1 highly ^[5] 177:16 204:1 282:9 298:5 366:1 Hilton ^[1] 1:9 himself ^[3] 17:19 19:9 375:10 hinge ^[1] 315:7 hinged ^[1] 315:8 hip ^[1] 351:11 hippocampus ^[3] 190:22 225:3 261:3 Hirsch ^[22] 2:15 6:20,20 216:10,11,16,21 217:5 321:10,11,20 328:22 329:11,14,14 335:16,21 337:8 343:1 348:10 370:16 384:22 his ^[11] 17:20 18:5,7 24:2 25:1 50:13 92:1 118:14 119:9 127:7 172:13 Hispanics ^[1] 382:10 histopathological ^[3] 216:19 217:3,17 historically ^[1] 31:18 histories ^[1] 275:11 History ^[62] 23:14 47:14 103:18,19 104:2,15 105:4,15,22 106:4,11,14,17,19,22 107:4,19 108:3,8,11 113:13 117:22 118:10,10 123:9 129:8,11 139:16 144:21 145:4 147:13 149:9 166:2 167:8 238:3 255:20 266:4 268:6 274:16,17,19 275:13,16 279:12,18,22 280:1,7,10 317:13 318:2,10,12,17 341:5,9,12,15 350:20,22 354:18,22 hit ^[2] 240:11 380:17	hoc ^[1] 362:13 hold ^[2] 89:19 185:8 homeostasis ^[1] 186:22 homeostatic ^[2] 213:17 225:14 homology ^[1] 203:1 homomeric ^[1] 195:10 honest ^[1] 352:7 honestly ^[1] 321:18 hope ^[3] 138:9 301:2 335:13 hopefully ^[3] 37:8 235:4 370:8 hopeless ^[1] 150:2 hopelessness ^[1] 119:5 hormone ^[2] 365:9,10 hormones ^[1] 188:9 Hospital ^[4] 8:5 102:3 158:2 228:5 hospitalization ^[10] 123:17,20 125:4,12 181:8,8 268:9 274:17 346:6 352:12 hospitalizations ^[4] 104:10,20 105:7 107:15 hospitalized ^[1] 113:19 host ^[1] 262:21 hostility ^[1] 18:7 hour ^[1] 184:10 hours ^[2] 12:6 119:8 house ^[1] 119:9 how ^[42] 16:11 18:14,22 29:2 33:19 133:7 140:18 142:4,4 143:13 155:8 162:14 165:15 171:3,18 178:12 180:2 192:1 231:18 232:20 237:4,16 258:11 279:15 296:12 306:15 307:19 313:2,3,4 314:12 315:11 351:5 357:3 360:21 363:16 366:21 370:1 377:10 378:16 379:17 382:6 however ^[24] 5:17 51:12 54:10 56:19 58:13 61:12 99:11 116:5 119:4 129:8 137:4,18 151:12 179:11 255:10 266:18 272:13 275:19 280:21 298:13 307:4 330:11 332:5 334:14 huge ^[6] 171:5 229:16 309:18 324:4,7 342:5 HUMAN ^[24] 1:1 57:4 61:2,14 164:4 205:17 206:1,5,10,21 207:3,3 208:5,13 210:1 211:1,6 212:22 222:10 231:5 247:17,21 250:8 326:15 humans ^[14] 68:19 74:20 208:12 211:16 231:21 232:18 233:15 248:14 249:14 270:8,10 326:10,21 364:17 hump ^[1] 359:17 hunger ^[3] 75:5 174:5,8 hydrolysis ^[1] 188:12 hyperactivity ^[1] 50:2 hyperalgesia ^[1] 60:20 hyperesthesia ^[2] 200:5 202:8 hyperexcitability ^[4] 200:7 202:9 231:14 269:18 hyperlipidemia ^[1] 161:1	hyperphasia ^[1] 65:15 hypertension ^[9] 73:5 79:2 91:18 147:3 160:2 161:1 162:6 244:10 368:8 hypertensive ^[1] 234:6 hypesthesia ^[1] 262:18 hypnotic ^[2] 281:2,8 hypnotics ^[1] 273:9 hypocaloric ^[3] 76:19 252:22 253:1 hypoglycemia ^[5] 99:12,20 100:3,10 183:4 hypoglycemic ^[2] 99:17 381:21 hyposeizures ^[1] 136:12 hypotension ^[1] 233:21 hypothalamic ^[2] 187:11 225:4 hypothalamus ^[6] 51:21 61:9 67:7 191:4,6 261:3 hypothesis ^[2] 289:22 291:22 hypothyroidism ^[1] 183:4 <hr/> I ^[744] 5:1,5,5,8,12,20,22 6:5,5,6,8,10,12,14,17 7:12,12,18,22 10:14,16,17 11:1 13:13,16 14:19 15:10,14,15 16:2,3,4 17:14 19:6 21:6 23:10,16 27:1,3,5 29:10,17 33:17,19 34:8 35:10,22 36:6,10,21,21 37:1,20 40:20 41:19 42:11,15 43:10 44:5,15,17,22 49:15,20,22 50:4 53:13 67:2 69:1,11,14 74:15,22 77:1 80:16 84:16 90:19 92:22 93:2,11,13,21 94:1,8,10 97:7 98:6,8,11 105:12 106:6,9,10 108:18,21 109:19 111:8 117:16 120:3,22 128:8 129:5,14 130:22 131:5 132:11,12 134:4,14 135:9 136:7 137:8,14 138:9,9 140:3 141:14 142:14 143:18 144:8 146:13 149:5 150:11 151:19 152:9,20 155:1 156:4 157:2,2 158:13,15 159:3 162:13 163:13 166:6 167:3 168:7 169:20 170:2,13,15 171:13 172:10,10,12 173:9 174:11 175:10,20 176:6,6 177:1,4,6,20 178:1,1,11 180:2,4,10,12,13 181:11,12,13,16 182:6,7,22 183:1,6 184:7 185:12,19 187:13 195:5 203:12,15 207:6 213:10 215:2,17 216:6,6,14 217:22 218:12,20 219:7,13,16,17 222:1,4,15 224:1,7 225:1 230:10,21 231:14 232:3,20,20,21 233:4 234:21 235:2,15,17,20 236:2,4 237:10,11,14,20,22 238:2,2,3,4,4,5,6,8,9,10,13,14,18,21 239:3,12,16,19 240:9,10,16,17,18,20 241:3,6,9,9 242:5,8,15,19,21 243:11 246:1 247:3,5 248:11,15,18 249:5,5,7,7,9,19 250:13,15 251:12,16,18 252:16 256:
--	--	--	--

<p>2 257:2 258:6,11 263:16 265:22 267:14 275:19 284:1 285:6,12,19 286:8 287:2 288:8 290:14,21 293:10,20 294:4,15 295:7 299:3,17,22 300:2,13,19 301:1,2,4 302:1 303:6,7,9,10 304:14,15,18 305:7,16 307:4,13,21 308:3,4,4,5,8,12 309:2,11,16,18,20 310:21 311:5,16 312:7,8,13,13,15,17 313:2,7,7,12 314:9,15,18,21 315:2,8,14,17,17,22 316:20,22,22 317:11,16,18,18,21 318:15,20,22 319:2,5,8,21,21 320:8,9 321:11,13,14,16,17,17,18,20,21 323:1,4,6,11,14,15,22 324:7,9,11,17 325:3,4,7,11,13,18,22 326:14 327:1,12,14,15 328:17,22 329:8,11,14,16,17,18,19 330:2,4,10,11,12,13 331:1,13,17,17,20 332:5,5,15,19 333:20,22 334:1,5,8,14,16,21 335:7,7,8,10,11,12,13,14,17 336:1,9,9,10,14,19 337:4,10,13,13,18,19,19,22 338:5,7,7,8,12 339:3,4,9,19 340:1,4,7,10,14,17 341:1,6,7,20,22 342:3,11,16 343:1,2,2,3,9,22 344:17,18,22 345:3,4,18,22 346:9 347:1,2,4,6,6,8,11,14,15,18 348:8,11,16,21 349:2,7,8,10,11,16,17,17,18,21 350:4,5,8,12,14,17,19 351:1,2,3,4,7,9,14,16,17,20 352:1,3,5,7,7,9,12,15,18,20,21 353:9,10,11,11,12,18,19,20 354:1,4,5,8,14,18 355:2,7,7,15,17,19,19 356:1,5,10,13,20,20 357:2,7,10,11,14,22 358:9,9,12,12,15,16 359:3,3,5,5,6,8,15,19 360:1,1,2,6,10,19,20 361:1,2,3,5,8,10,11,13,18,19,19,20,20,22 362:1,4,5,7,12,17,18 363:8 364:8,9,13 365:2,3,16,17 366:7,8,11,14 367:4,6,19,19,21 368:4,9,11,17,22 369:4,11,15,20 370:3,6,11,11,12,12,12,19,21 371:2,5,13,16,22 372:1,4,4,9,11,12,13,14,18,19,20 373:1,7,8,13,15,20,21 374:2,11,12,15,16,22 375:3,6,6,6,14,17 376:3,5,18 377:13,15,17,19,19,20 378:4,10,12,21 379:6,9,10,15,16,20 380:1,2,10,11,16,17,18 381:4,6,11,15,17,20 382:1,4,7,12,14,21 383:1,4,6,6,10,12,13 384:22 385:3,3,4,9,13,14,14,15,19</p> <p>I'm [2] 274:20 384:21</p> <p>IC50s [2] 199:1,4</p> <p>ID [1] 21:10</p> <p>idea [9] 65:22 121:18 224:9 239:7 242:10 334:7 335:6 354:17 370:1</p> <p>ideation [43] 22:5 24:15 29:22 30:17 31:6 33:2,4,10 35:9,12,20 102:19 112:12,21,22 113:6 119:19 120:10,21 121:16 122:3,6,11 135:18 137:16,20 266:7 282:13 283:18,20 285:9 291:3,7 292:21 293:18 296:12,15,18,20 297:15 314:22 340:13 361:4</p> <p>ideations [2] 285:1,4</p> <p>identical [2] 80:5,19</p> <p>Identification [2] 15:6 152:21</p> <p>identified [23] 38:13,16 41:13 46:17 110:12,15 130:6 138:13 140:8,21 141:1 155:14 156:16,18 157:9 189:2,5 230:18 283:14 297:9 298:1 312:4 362:15</p> <p>identifies [1] 139:13</p> <p>identify [13] 102:5 107:10 152:10,20 159:11 184:15,18 203:12 269:8 329:12 354:6 356:9 381:9</p> <p>identifying [2] 148:14 354:17</p> <p>If [150] 12:5,20 13:8 18:9 33:16,17 34:5 54:5 56:2,19 57:13 58:10 60:9 61:19 68:18 89:17 96:20 97:2 103:1 106:13,18 108:7,11 110:20 112:1 121:8 130:11,19 133:4,16,18 137:22 139:22 150:7 154:12 170:9 174:17 175:3,10 178:5,11 181:6,12,14 182:7,11 184:4,12,20 185:12 199:1 201:20 202:5,11 203:9,15 205:14 206:5,19 208:22 209:2,6,9 210:11,16 212:9 213:10 214:2 216:1 217:17,22 218:8 223:5,12,13 228:22 229:12 232:14 235:3 236:12 237:15,22 239:21 241:6,8 247:20 248:6 258:3,4 266:21 275:4 280:22 287:14 289:22 291:17,20 292:17 300:14 301:7 303:2 306:9 308:4 316:17 317:16 318:14 319:8 321:18 324:3 326:8,19 329:11 330:19 332:6 333:15 334:20 335:11 337:3 338:7,14 339:8,9 340:5 341:15 344:9 345:9,13,14,18 359:12,16 360:6 361:2,19 366:20 367:9 370:22 373:9 374:1,3,20 376:18 377:10 378:21 379:4,11 380:3,20 383:3 385:5,19</p> <p>Ignoring [3] 254:14 284:16 317:1</p> <p>Il [14] 6:7 40:6 75:8 94:1,11,12 109:7 110:7,12 112:15 129:6,14,17 259:8</p> <p>III [17] 39:9 40:20 75:18,22 93:18 94:16,21 95:14 110:7 112:15 129:6,14 136:20 180:19 259:8 260:21 338:18</p> <p>III-B [1] 265:8</p> <p>IIIb [1] 119:14</p> <p>illness [43] 113:12 355:1</p> <p>illnesses [1] 239:16</p> <p>illustrates [2] 263:2 285:11</p> <p>illustrative [1] 262:8</p> <p>image [1] 42:7</p> <p>imagine [1] 233:22</p> <p>imaging [2] 265:20 266:15</p> <p>imbalance [14] 112:22 119:20 120:11 121:15 122:2 125:22 135:14,17 136:13 272:13,21 278:1 300:19 313:17</p> <p>Immediately [1] 44:4</p> <p>imminent [1] 285:3</p> <p>imminently [1] 181:9</p> <p>immune [3] 187:12 189:4 226:3</p> <p>impact [3] 72:12 165:5 309:18</p> <p>impair [1] 225:18</p> <p>impaired [5] 70:13 72:22 200:4 202:4 268:15</p> <p>impairment [12] 124:2,18 125:10 260:16 262:4 263:3,8 264:6 268:15 305:19 342:3 358:22</p> <p>impairments [1] 262:19</p> <p>impairs [1] 244:7</p> <p>implantation [1] 231:17</p> <p>implantations [1] 231:4</p> <p>implement [1] 157:14</p> <p>implementation [1] 145:20</p> <p>implemented [2] 101:15 167:17</p> <p>implementing [1] 121:4</p> <p>implicated [5] 187:5 189:4 191:5 216:15 269:12</p> <p>implication [1] 350:4</p> <p>implications [1] 53:21</p> <p>implied [1] 368:11</p> <p>implies [1] 349:6</p> <p>importance [2] 101:5 229:5</p> <p>important [62] 10:20 13:16 14:16 18:14 33:3,13 47:11 50:19 52:20 54:15 55:4,17 59:9 60:9 74:9 81:21 84:7 85:16 97:5 102:7 103:1 113:5 119:11 120:6 122:5 123:17 125:3,11 133:22 136:14 162:13 163:19 181:7 182:14,22 184:7 188:4 190:13 198:15 199:16 206:12 207:13 209:22 222:20 231:22 253:18 254:10 271:8 273:13 294:4 328:13 334:10 344:18 345:4 346:5 348:15 354:10 372:17 373:2 382:5 383:1,2</p> <p>Importantly [3] 92:17 139:13 165:10</p> <p>impossible [1] 303:17</p> <p>impressive [1] 365:22</p> <p>improve [2] 13:10 297:6</p> <p>improved [8] 32:19 66:21 67:16 88:4 90:22 92:8,16 375:15</p> <p>improvement [23] 66:16 69:16 72:7 87:3 89:2 90:2,12,16 91:10,22 92:5,12,20 164:14,19 165:6,8 172:5 178:15 179:1,2 357:19 358:6</p> <p>improvements [5] 87:19 165:1 253:8 265:2 299:14</p> <p>improves [7] 68:12 72:10 161:5,6 168:13,14 244:18</p> <p>improving [1] 32:16</p> <p>impulsivity [1] 273:19</p> <p>in [1235] 5:14 6:18 8:22 9:2,6,11,19 10:4,22 12:13,15 13:4 15:1,4,6,12 16:9,10 17:3,5,15 18:1,12 19:9,10 20:6 22:9 23:6,6 24:2,10 25:5,14 26:1,4 27:12,20 28:3,7,9 29:16,16 30:3,12 31:1,4,18,18,21 32:3,9 33:10,14 35:5,7,9,21 37:4 38:2,12 39:1,2,9,11,12,14,15 40:2,5,6,8,14,15 41:3,5,9,13,21 42:7,14,21 43:3,3,11,12,12,13,15,16,17,20,22 44:4,5,12,16,21 45:3,4,5,7,13 46:11,15,16,18,18 47:3 48:3,9,10,12,18 49:6 50:3,6,15 51:1,1,11,13,17,21,22 52:4,12,18,19,21 53:6,13 54:2 55:1,15,18 56:4,8,10,12,14 57:3,5,8,11,12,13,19,20,20 58:1,7,11,12,16,22 59:1,2,7 60:13,22 61:7,9,14,17,21 62:1,17,17,18 63:2 64:11,14,17,18,21 65:4,13,14,16,18,19,20 66:3,5,17,20 67:5,7 68:8,13,19 69:13,19,20 70:2,3,4,6 71:3 72:7,16,19,19,21 73:9,15,18,19 74:20,22 75:4,5,6,9 76:1,2,7,11 77:13,14,14,15,16,17,19 78:1,15,16,18 79:2,9,10,13,18 80:5,10,14,21 81:1,5,6,8 82:5,6,10,15,16,21 83:1,5,7,10,11 84:1,2,3,10,15,15,20 85:15,20 86:9,10,11,16,19,21,21,22 87:1,14,16,19 88:1,10,15,17,19,20 89:13,16,19 90:2,9,12,16,20,21 91:10,14,22 92:4,5,9,10,18,19,21 93:4,12 94:10,11,12,14,16 95:4,7,19 96:20 97:1,12,20 98:4,7,9,15,15,20 99:10,18,19,22 100:6,8,12 101:6,8,22 102:9,19 103:3,13,19 104:2,17 105:13,16,19,21 106:2,3,8,11 107:5,7,18,21,22 108:6,13 109:2,3 110:12 111:17,17,19 112:10,15 113:1,6,12 114:1,8,12,16,20 115:3,6,11,12,21 116:1,6,6,19 117:3,4,6,8,10,17 118:21 119:9,10,20 120:5,8,9,15,15,19 121:1,2,13,16,18,19,20,21 122:2,4,6 123:13 124:10,15,18 125:1,5 126:5 127:2,11,18 128:7,10,11,20 129:6,10,12,16,18 130:9,17,20 131:20 132:4,5,6,8 133:21 134:10,19,22 135:2,4,7,9,18 136:1,9,13,21 137:17 138:7,12,17,19 139:1,6,9 140:11,12 141:2,8,14 142:14 143:17,18 144:4,7,9,9,10,10,13,18 145:7,11 147:22 149:6,15 150:5,14,15,21</p>	
--	--

<p>151:2,21 152:3,5,12 154:21 155:20,21 156:2,10,11,16,21 157:8,9,17 158:4 159:6 160: 13,18 161:3,7,12,17 162:8,17, 20,21 163:13,16 164:2,10,13, 14,18,19 165:1,6,8,18 166:1, 3,7,9,11,22 167:3,4,5,9,13 168:7 169:10 170:18,18 171: 14,16 172:21 173:2,3,3,7,21 174:13 175:14 176:5,6,7,11, 13,20,22 177:4,8,9,12 178:4, 8,9,15,20,21,22 179:17,18,19, 22 180:19 182:18 183:1,8,17, 18 184:3,5,8 186:8,11,16,17, 20 187:3,5,8,15 188:7,9,11, 14,15,19 189:4,6,7,12,12,13, 13,13,18 190:7,7,11,13,18,22 191:2,3,5,6,12,15,16 192:15, 21 193:2,21,22 194:1,21 195: 17 196:10,16 197:1,1,6,8,10 198:15,22 199:11,12,15,19 200:3,10,11,16,20,21,22 201: 1,2,3,5,7,8,19 202:1,3,7,9, 21 203:1,4,8,16,19 204:7,12, 14,15,16,16,22 205:15,18,21 206:2,13,22 207:9,13 208:2,2, 4,4,10,12,15,20,22 209:9,17, 20 210:9,22 211:4,5,7,11,12, 16,21 212:5,13,14,19,21 213: 7,11,21 214:10,10,20 215:1,2, 11,11,22 216:19 217:8,10,10 218:2,17,18,19 219:1,19 220: 11,17 222:16 223:9,20 224:4, 12,17,19,20 225:5,9,13,17,17, 20 226:6,12,16,17,18,19,20, 22 227:5,5,6,9,9,13 228:4,7, 21 229:5,13,18,20 230:12,14, 18 231:2,3,4,6,8,9,9,12,13, 21,21 232:6,9,10,18 233:4,7, 11,15,16,20 234:2,3,10,11 235:2,13,21,22 236:2,5,6,19, 21 237:13,14,16 238:16 239: 2,10 240:4,6,11,18,19 241:9, 14,22 242:4,5,8,11,16,20 243: 21 244:12,17,22 245:16,21 247:8,18,22 248:4,13,14 249: 2,13,14,17,21,22 250:4,7,7 252:14,15 253:6,8,10,14,19, 20 254:10,19 255:11,13,14, 18,18,22 256:5,8,9,15,20 258: 2 259:1,20 260:9,13,17 261:2, 7,12 262:7,10,10,14,19 263:4, 8,9,11,14,15 264:3,4,8,20,21 265:2,6,8,10,16,18 266:5,18 267:5,12,17,18,19,20 268:3,5, 10,17 269:5,12,15,16 270:5,6, 8,10,21,22 271:2,3,6,11,19 272:1,3,9,21,21 273:14,16,18 274:1,3,12 275:6,11,17 277:1, 3,4,10,16 278:4,14,17 279:4, 11,21 280:2,4,9,14 281:6,17 282:1,6,6,9,12,13 284:3,4,6, 11,14 285:7,7,8,13,15 286:10, 14,17,19,21 287:1,19,21 288: 15,16,18,22 289:2 290:1,2,4, 6,10,10 291:10,12,19 292:3, 10,13,14,16,19,21 293:1,2,10,</p>	<p>19 294:3,17,17,18,18 295:7,8, 10,18,22 296:16 297:11,14, 16,18,18,22 298:4,5,7,11,12, 21 299:10,13,14,19 300:6,10, 16,17 301:18,19 302:1,16 304:22 305:11,20 306:17 307:9 308:6,13,16 309:3,9,10, 12,14 310:4,7,9,10,14,16 311: 5,7,22 312:4,8,9,15,22 313: 20 314:9,10 315:16 316:2,6,6, 21 318:16 319:19 320:10,15, 21 321:3,3,4,22 322:6,10,14, 15 323:7,19 325:4,15 326:2,5, 9,10 327:16,18 328:3 329:4,5, 15 330:7,18 331:2,9,16 332:1, 11 333:4,14 334:6,10,18 335: 1,5,6,14,17 336:12,13,19 337: 5 338:18,19 339:12,21 340:9 341:3,16,18,19 342:13 343:5, 12 344:4,5,9,13 345:16 346:9, 14,14 347:3,5,5,6 348:19 349: 3,4 350:22 351:12 352:5,12, 16,17 353:2,8 354:15,19,22 355:4,6,11,14,21 356:10 357: 3,5,9,17,21 358:5,9,18,22 359:9,11 360:8,11,13,14,16, 18,20 361:15 362:15,15,18 363:21 364:7,15,17 365:7 366:4,12,15,18,20,22 367:8, 14 368:10 369:2,18 370:5,14 371:1,5,8,9,14 372:13,15 373: 5,8,17,19,19,22 374:3,14 376: 1,3,5,7,14,16,16,16 377:16, 18 379:19 380:2,3,7,14,14,19 382:5,10,21 383:8,17 385:17 in-depth [1] 100:21 inactivate [1] 56:11 inactive [4] 55:15 112:2 196: 22 198:10 inadequate [2] 39:13 342:6 inappropriate [2] 48:2 145:3 inappropriately [1] 17:8 inbred [2] 216:2,3 incidence [16] 72:21 99:15 115:20 122:21 126:10 131: 16,18 165:22 208:19 209:17 227:19 228:15 249:18 272:2 279:20 285:20 incidences [2] 202:4 277:15 inclined [1] 363:22 include [25] 37:12 48:12 95:9 141:9 148:18 155:10 160:12, 13 186:2 200:4 212:3 223:8 225:13,15 268:2 272:11 276: 13,18,21 277:9 297:11 324:5 344:21 345:15 363:11 included [28] 38:6,10 45:14 76:9 96:18 97:16 109:7 110: 7 120:5 130:15,20 131:3,4 137:6 147:20 156:20 173:2 259:8 260:9,10 276:15 282:2 283:15,20 284:22 311:22 316:21 320:18 includes [4] 124:4 133:3 168: 20 256:6 including [55] 41:13 51:20 52:5,10 58:3 59:13 67:11,16</p>	<p>72:11 87:12 94:4,13 102:18, 21 110:8 116:4 120:20 129: 15 132:15 146:5,20 147:2 153:14 163:5 165:6 167:1 171:17 186:20 187:9,20 188: 1 189:14 191:13 194:1,6,9,16 202:19 204:11,12 206:9 224: 15 231:11 237:13 243:2 245: 1 256:12 258:14,15 260:15 273:5 284:15 305:19 331:16 357:21 inclusion [1] 117:20 inclusion/exclusion [1] 31: 17 inclusive [1] 376:3 inconclusive [1] 29:8 inconsistent [1] 115:13 incontinence [1] 320:14 incorrect [2] 16:22 173:18 increase [36] 43:3 58:12 59:2 64:18 70:3 82:16 83:5 88:19 101:22 127:1 192:21 195:13 202:9 209:20 227:5,13 239: 11 269:14 273:1 279:18 282: 1 288:20 292:13 293:1,2 297: 16,17,18 300:17 310:9 322: 13,17,19 326:9 343:12 344:9 increased [30] 61:17,21 62:4 64:10 67:17,18,19 88:17 97: 22 132:8 134:12 136:17 140: 11 162:2 183:3 190:1 200:6 226:14 227:16 231:6,7 233:9, 13 269:16 288:4,17 289:2,4 290:1 292:20 increases [8] 61:10 68:10 88: 15 226:17,18 227:4 228:21 244:8 increasing [4] 54:6 55:2 56: 10,21 incubated [1] 64:10 Indeed [8] 38:8 47:8 165:4 166:22 187:1 279:20 291:17 312:20 independent [8] 25:21 100: 18 136:22 193:22 197:17 198:12 332:4 373:5 index [3] 13:5 212:6,11 Indiana [2] 37:15 49:4 indicate [7] 154:2 173:3 174: 1 217:6 291:15 354:21 355:4 indicated [15] 17:22 58:6 96: 6 110:3 113:10 141:2 187:22 188:21 201:2 228:11 248:21 266:16 291:11,14 374:15 indicates [4] 195:3 276:2 280:5 292:20 indication [18] 13:4 43:16 44: 1 46:16 48:2 74:16 85:14 90: 5 92:19 205:6,9 242:7 251: 18 311:9 328:19 339:4,7 383: 16 indications [6] 41:6 46:16 93: 20 95:9 166:14 233:1 indicative [1] 290:20 indices [1] 173:12 individual [8] 111:11 259:20, 21,22 306:4 352:13 376:4</p>	<p>383:11 individual's [1] 222:21 individually [1] 265:17 individuals [11] 11:5 13:4 94: 9 167:13 222:4 227:21 245:5 279:14 287:22 332:12 383: 17 induce [2] 216:5 230:17 induced [4] 83:9 92:4 210:19 211:10 induces [1] 75:16 induction [3] 192:3 210:5 216:1 Industry [9] 2:19 8:7 9:3,4,6 14:5 32:3 235:13,14 ineffective [1] 246:6 inevitable [1] 330:20 infarction [2] 117:20 299:11 infer [1] 349:5 inferred [1] 24:12 infertility [1] 70:19 inflammation [4] 59:19 60: 17 66:18 267:10 inflammatory [4] 60:19 161: 6 164:21 226:3 inflate [1] 324:22 influence [5] 65:1,6 116:3 211:9 226:3 influenced [1] 365:21 inform [3] 32:20 65:12 120: 22 informal [1] 235:15 information [68] 13:9 22:11, 21 23:7 30:22 31:10 35:1 37: 9 40:16 44:2,12 45:16,17 46: 6,13 109:1,3 117:12 119:17 120:4 128:16,16 130:9,11 133:22 136:5 144:15 146:3 147:19 149:3,15 150:17 163: 8 214:13 218:14 222:17 223: 7 228:5,20 267:16 285:2,5 302:5 303:12 304:11 308:10 321:9 338:8,17,19 342:4 343: 19 353:4 368:17,20 371:13, 16,20 372:9 374:1,17,20 375: 21 377:3 378:13 381:16 385: 7,12 infrequent [1] 125:22 inhibit [3] 43:5 58:4 195:18 inhibition [2] 193:9,11 inhibitor [1] 183:12 inhibitors [1] 43:2 inhibitory [3] 52:1 193:8,16 inhibits [1] 224:22 initial [12] 84:22 145:22 167: 20,22 175:22 176:8,15,20 177:9,15 244:21 252:14 Initially [2] 282:14,18 initiation [2] 148:2 150:9 Initiative [1] 298:16 injuries [2] 20:21 25:12 injury [3] 19:10 24:1,4 innervate [1] 52:5 innervating [1] 67:9 input [2] 192:8 299:22 insert [4] 44:2 137:13 152:19 153:8</p>
---	---	--	---

<p>inserted ^[1] 162:22</p> <p>insightful ^[1] 381:7</p> <p>insights ^[1] 169:3</p> <p>insignificant ^[1] 261:17</p> <p>insisted ^[1] 287:7</p> <p>insomnia ^[6] 99:6 226:17</p> <p>227:11 273:6 276:18 297:13</p> <p>Instead ^[3] 58:13 133:5 302:19</p> <p>Institute ^[7] 7:14 15:1 144:4</p> <p>148:17 149:1 151:7 156:3</p> <p>Institute's ^[1] 9:14</p> <p>institution ^[2] 281:7,11</p> <p>instructed ^[1] 6:4</p> <p>instrument ^[2] 91:6 178:19</p> <p>instruments ^[1] 90:21</p> <p>insulin ^[2] 67:16 297:8</p> <p>insurance ^[2] 144:1 240:16</p> <p>intact ^[1] 307:11</p> <p>intake ^[15] 61:10 63:6,10,19</p> <p>64:4 67:6,13 68:1,9 75:6 186:21</p> <p>189:18 190:2 200:10,22</p> <p>integrated ^[1] 138:11</p> <p>integrates ^[1] 68:1</p> <p>intend ^[2] 170:21 352:19</p> <p>intended ^[4] 42:8 47:3 152:4 311:8</p> <p>intent ^[9] 22:13 23:20 24:7,11</p> <p>30:19 36:2 120:7,9 353:11</p> <p>intention-to-treat ^[1] 254:21</p> <p>intentional ^[1] 18:2</p> <p>inter ^[1] 193:18</p> <p>interact ^[2] 53:5,9</p> <p>interaction ^[3] 193:10 255:11,16</p> <p>interactions ^[6] 43:6 45:9</p> <p>195:6,8 199:9 201:6</p> <p>interacts ^[1] 199:22</p> <p>intercellular ^[2] 186:15 192:21</p> <p>Interest ^[19] 3:5 8:12,14,16,21</p> <p>9:22 10:4 94:4 100:22</p> <p>101:3 118:17 135:7,7 150:5</p> <p>162:20 224:8 258:21 263:11 283:5</p> <p>interested ^[5] 36:20 321:22</p> <p>349:1 360:14 374:3</p> <p>interesting ^[18] 18:16 25:7</p> <p>26:3 58:20 88:20 175:2 225:8,16</p> <p>232:2 234:1 289:21 296:22</p> <p>300:16 316:2,10 334:9 352:10 375:16</p> <p>interestingly ^[1] 191:5</p> <p>interests ^[2] 8:20 9:6</p> <p>Internal ^[2] 48:14 69:2</p> <p>internally ^[2] 339:19 376:6</p> <p>International ^[1] 95:2</p> <p>internationally ^[2] 32:4 34:18</p> <p>Internet ^[1] 230:13</p> <p>interneurons ^[1] 192:17</p> <p>interpretable ^[1] 18:15</p> <p>interpretation ^[2] 95:4 345:14</p> <p>interpreted ^[3] 138:17 178:12 373:5</p> <p>interpreting ^[2] 17:4 360:6</p>	<p>interval ^[13] 116:14 126:21</p> <p>131:21 272:6 315:11,15,21</p> <p>316:1 317:3,6 324:6 325:11,18</p> <p>intervals ^[3] 26:15 156:10 316:18</p> <p>Intervention ^[6] 7:14 32:9 71:5</p> <p>140:16 156:19 347:22</p> <p>interventions ^[1] 141:5</p> <p>into ^[28] 16:5 22:1 23:10 34:6</p> <p>103:12 118:9 137:8 155:5</p> <p>159:1 161:2 171:10 179:12</p> <p>182:7 198:18 220:13,17 230:10</p> <p>242:10 254:15 283:7 296:3</p> <p>314:20 315:1 326:9 333:21</p> <p>334:4 336:12 364:8</p> <p>intolerable ^[1] 245:6</p> <p>intolerance ^[4] 73:1 331:19 332:2,13</p> <p>intra-cellular ^[1] 193:19</p> <p>intrinsic ^[2] 197:7,10</p> <p>introduce ^[11] 49:2,21 69:1</p> <p>93:2 155:4 157:20 222:4 235:9</p> <p>250:13 254:15 351:22</p> <p>introduced ^[1] 283:1</p> <p>introduces ^[1] 115:13</p> <p>Introduction ^[6] 3:12 5:10</p> <p>10:10 36:13,17 97:21</p> <p>Introduction/Background ^[2] 3:7 10:12</p> <p>Introductions ^[3] 3:4 5:21 6:3</p> <p>introductory ^[2] 37:13 157:3</p> <p>inverse ^[31] 53:18,20 54:13,15,18,19</p> <p>55:2,5,7,10,11,13,14,18,20</p> <p>56:1,3,16 57:1,6,14,14 58:11</p> <p>196:17,18 197:4,9 198:5</p> <p>238:9 274:9 324:22</p> <p>inversely ^[1] 273:22</p> <p>invest ^[1] 240:18</p> <p>investigate ^[1] 282:19</p> <p>investigated ^[2] 322:5 362:14</p> <p>investigating ^[1] 61:1</p> <p>investigation ^[11] 71:7 189:3,17</p> <p>200:19 220:9 266:16,20</p> <p>268:18 287:7 306:20 307:3</p> <p>investigations ^[2] 124:5 271:12</p> <p>investigator ^[11] 34:15 101:19</p> <p>102:5,22 117:1,2 119:3</p> <p>125:11 167:3 306:7,8</p> <p>investigators ^[8] 21:16 98:7</p> <p>102:2 107:8 123:3 129:22</p> <p>306:17 370:5</p> <p>investment ^[1] 236:19</p> <p>involve ^[2] 9:19 151:20</p> <p>involved ^[16] 59:7 183:14</p> <p>187:8,15 188:14,15 190:18,22</p> <p>191:2,11,12 196:4 203:19</p> <p>225:12 242:3 273:18</p> <p>involvement ^[3] 10:6 119:10</p> <p>181:1</p> <p>involves ^[3] 158:20 198:5 204:7</p> <p>involving ^[2] 156:5 244:4</p> <p>ion ^[3] 53:6,8 194:22</p>	<p>IRB ^[1] 287:6</p> <p>ironic ^[1] 337:10</p> <p>irritability ^[1] 118:1</p> <p>is ^[1097] 5:21 8:16 9:2,5,8,12</p> <p>10:20,22 11:2,5 12:11 13:8,16</p> <p>14:21 16:9,16,18,19 17:3,6,22</p> <p>18:5,15,16,16,17,21,21</p> <p>19:8 20:1,3,8 21:1,17,19 22:4,19</p> <p>23:18,21 24:3,4,11,15,18</p> <p>25:8 26:3,3,18 27:3,9,12,14,22,22</p> <p>28:1,19 29:5,7,11,13,15,15,18,19</p> <p>30:6,17,22 31:2,3,4,9,15,16</p> <p>32:19,21 33:3,4,4,7,13</p> <p>34:1,8,12,14,20 35:14,21</p> <p>36:6 39:21 40:3,14,16 41:10</p> <p>42:1,3,7,17,18,22 43:2,11,16,21,21</p> <p>44:11,13,18,19,20</p> <p>46:6 47:1,3,8,9,11,11,13,13,21</p> <p>48:2 49:3,7 50:22 51:5,13,15,22</p> <p>52:3,4,21 53:13,18,21</p> <p>54:2,5,15,21,22 55:4,7,8,9,13,16,18</p> <p>56:3,5,7,13 57:4,12,14,17,21</p> <p>58:1,4,6,12,14,16,18,19</p> <p>59:6,7,9 60:1,2,9,10,11,13,21</p> <p>61:2,14 62:6,13,17,20,22</p> <p>63:7,10,11,13,18 64:4,8,13</p> <p>65:2 67:3,12,22 68:7,15 69:18,19,22</p> <p>70:3,7,10,13 71:6,16,17,20</p> <p>72:1,6,17 73:1,4,7,8,11,12,13,14</p> <p>74:3,10 80:21 81:4,6</p> <p>82:22 84:8 85:9,21 86:19</p> <p>87:3,6,6,8,8,17 88:5,9,16,19</p> <p>89:6,7,16,18 90:4,13,17 91:13,15,19,21</p> <p>92:3 93:3,13 95:15</p> <p>97:5,10 102:7 103:1,10,14</p> <p>104:11,18 105:1,2,2 106:4,12,13,17</p> <p>107:22 108:6,10,11,15</p> <p>109:15,19 111:7,21,22 112:1,2,7,20</p> <p>113:5 114:8,16,17 115:9,15,15</p> <p>118:16 119:1 120:1,6,11,16</p> <p>121:1,9 122:5 124:21 126:12,20</p> <p>127:1,6,21 128:17,19 130:2,14</p> <p>131:2,11,16,18,22 132:1,6,6,13,22</p> <p>133:1,4,8,13,16,17,22</p> <p>134:11,11 135:4,7 137:2,12,13,14</p> <p>138:5,22 140:5 142:1,8,10,17,21</p> <p>143:3,6,7,17</p> <p>145:4,7,17,18,18,19 146:18,22</p> <p>147:1,12,12,12,22 148:13</p> <p>149:4,5,17 150:4,8,12,12,22</p> <p>151:6,14,19 152:3,17,17,18</p> <p>153:11,12 154:1,7 155:2,2,4,9,16,19</p> <p>156:4,5,11 157:3,5,5,7,12,20,22</p> <p>158:8,17 159:17</p> <p>160:5,6,18,19 161:3,4,17,18</p> <p>162:10,13,14,18,20,21 163:19,22</p> <p>164:8,14 165:4,10,13,15</p> <p>166:11 167:21,21 168:1,4,17,19</p> <p>170:19,21 171:8,11,15,19,21</p> <p>172:8,17 173:2,9,14,16,17,18,18,18,20,21,22</p> <p>174:2,8,9,12,12,14,19,20</p> <p>175:6,7 176:4,5</p> <p>177:3,22 178:4,18 179:4,8</p> <p>180:3,12 181:17 182:14,19,19,22</p> <p>183:6,9,10,21 184:2,2</p> <p>185:4,5 186:14 187:7,19,22</p>	<p>188:4 189:11,19 190:1,6,6,12</p> <p>191:6,12,17 192:11,17 193:2,5,9</p> <p>194:5 195:5 196:4,21</p> <p>197:7,11 198:2,7,12,15,17,21</p> <p>199:2,7,18 200:6,9,17,18 201:3,11</p> <p>202:6,12,21 203:16,19</p> <p>204:2 206:12 207:8 208:3,14,15</p> <p>209:13,20,22,22 210:10,13,14,17,20</p> <p>211:21,22 212:8,8,20</p> <p>213:4 214:5,10 215:16,19,20</p> <p>216:11,12 217:11,18</p> <p>218:7 219:13,17,20,21,22</p> <p>220:3,4,8,11,12,13,16,19 222:12,20</p> <p>223:18 224:6,11,12</p> <p>225:9,16 226:10 227:3,17</p> <p>228:7,9,10,12,19 229:2,5,12,16</p> <p>230:20,21,22 231:20 232:2,3,5,9,12,14,19</p> <p>233:4,16,22</p> <p>234:12,17 235:5,8 236:1,9,11,11,11,16</p> <p>237:2,5,6,6,7,11,17,19,20,22</p> <p>238:1,7,8,9,11,12</p> <p>239:6,8,12,22 240:3,4,5,5,5,7,10,11,16,19</p> <p>241:5,9,13 242:3,4,12,12</p> <p>243:7,8,16 244:6 247:9,11,12,12,16,19,22</p> <p>248:1,7,12,18,18,19,21,22</p> <p>249:1,12,18,21</p> <p>250:3,5,6,8,9 251:3</p> <p>252:9,14 254:10,22 255:1,5,8</p> <p>261:2 262:17 263:3,18 264:7,14,18,21</p> <p>265:11 266:3,21</p> <p>267:2,15,15 268:10,22 269:13</p> <p>272:3,9 273:18 274:9,10</p> <p>276:4,6,19 277:22 278:5 280:9,11</p> <p>281:4 282:8 283:18 284:21</p> <p>285:22 286:1,21 287:5,6,14,16,17</p> <p>288:3,8,11 289:1</p> <p>290:2,5,7 291:2,3 292:2,3,6,7,8,11,15,15,22</p> <p>293:10,21</p> <p>294:4,5,9,19 295:6,7,20,21</p> <p>296:1,2,22 297:1,4,20 298:3,3,22</p> <p>299:4,5,10,11,12 300:8,13,16</p> <p>301:11,15,19,20,22</p> <p>302:9,22,22 303:5,7,7,15,17</p> <p>304:4,7,9,10 306:3,12,15,21</p> <p>307:1,5 308:12 309:2,14,17</p> <p>310:8,10,15,16 311:6,8,9,10,14</p> <p>313:7,8,19 314:9,11,19,21,22</p> <p>315:2,11,15,18,20 316:2,12,21</p> <p>317:5,14,17,19 318:22</p> <p>319:1,8,9,10,10,18 320:21</p> <p>321:7 322:13,18,22 323:1,17</p> <p>324:4,6,12,22 325:7,13 326:8,11,12,14,14,20</p> <p>327:12,17,19,20</p> <p>328:2,4,13,19 329:2,2,16,19,20,22</p> <p>330:2,6,8,8,9,12,13,16,20,21</p> <p>331:3,6,9,15 332:2,3,7,9,16,20,21</p> <p>333:5,16,16,18,18,19</p> <p>334:1,8,9,9 335:6,13</p> <p>336:1,10 337:1,6 338:11,17</p> <p>339:13 340:9,11,12,14,20</p> <p>341:4,22 342:7,14,19,19,20</p> <p>343:13,14,15,16,21 344:4,5,6,6,8,12,16</p> <p>345:3,9,12,14,21</p> <p>346:9,9,10,11,12,15,18,20</p> <p>347:21,22 348:8,9,17 349:9,12</p> <p>350:1,5,9,10,11,11,14,17</p> <p>351:5,8,11,12,13,18 352:2,</p>
---	---	--	---

<p>9,13,13,18,21 353:4,7,7,11 354:10,18,21 355:2,5,8,9,10, 17,20 356:4,5,9,16,21 357:4, 8,14,15,16,20 359:4,4,5,18, 19,20,22 360:1,10,11,12,13 361:3,5,11,12,16 362:6,9,12, 19 363:8,19 364:16,20,21,22, 22 365:15,15 366:3,3,6,6,9, 16 368:14 369:6,17 370:9,13, 13,14,19,21 371:8 372:7,8,10 373:1,2,17,18 374:5,9 375:18, 20,21,22 376:4,6,11,13,14,15, 15,18,22 377:18 378:4,13 379:2,4,5,10,11,12,14,15,20 381:3,4,11,15,17,19,22 382:7, 8,10,19 383:1,8,12 385:4,10, 14 ischemic ^[1] 124:17 isn't ^[4] 51:21 207:22 220:6 332:3 isolated ^[1] 113:11 isolation ^[2] 70:15 122:7 issue ^[16] 8:16 16:8 126:8 135:21 165:11 223:14 232:6 237:11 241:14 323:10,20 350:8 358:18 382:8,13 383:1 issued ^[1] 8:22 issues ^[21] 12:3,7,16 14:21 15:4 18:11 138:14 233:1 235: 16 237:11 251:13 306:22 329:7,9 336:7,8 339:20 352: 9 366:10 367:13 381:6 It ^[517] 10:20 16:9 18:10,17 20: 13,14 21:12 22:3 23:15,21 24:1,3,11,12,17,18,18 25:10 27:3,9,14,20 28:12,14,16,19 29:16,18,21 30:1,9,18 31:4, 15,16 33:3,4,12,13 34:1,1,2, 14 36:1,6,6 39:2 41:19 42:3, 17,18,19 43:11,14,21 44:20 46:7,16 47:11 48:4 49:2 51:5, 12,12,13 52:4 54:8,15,16 55: 4,8 57:5,9,10,12 58:12,17 59: 3,9 60:2,8,11 61:7 66:5 67: 10 68:10 69:19 71:20 72:5 80:21 81:2,4 89:6,7 91:15 92: 3 97:5 102:7 104:4,7,18,21 105:12 106:10 108:10,10,19 109:15 110:9 111:8,14,22 112:3 113:15 115:15 116:7, 20,20 117:1 119:7 120:5,16 121:15 122:5,7 123:19 124: 21 125:2,3,8 126:4,11,15 127: 9,15,21 128:17 130:11 131:4 132:4,5,6,13 133:7,13 137:13 138:8 140:8 142:18,20 143:7, 7,9 145:18 149:13,14,17,19 150:22 151:21 153:10 155:3, 9 156:5,22 157:5,19 160:6,8 161:5,9,19 162:14,14,17,20 163:19 164:1 168:11,12,13, 14,14 169:11 170:19,19 173: 17,20,22 174:3 177:4 178:3, 17 181:7,9 182:12,14,19,19 183:9,22 186:6 192:1 194: 5 196:21 197:6,11 198:15 199:2 200:18,20 201:6,7 203:</p>	<p>16 205:7 206:7,12,20 208:2, 15 209:22 210:13,14 211:22 215:18 217:18 218:13,20 219:1,13,18,22 220:12,16,19 222:20 223:15 225:20 228: 17,19,19 230:21 232:2,14 233:22 234:17 235:5,8 236:9, 11,11,18 237:2,5,6,8,17,20, 22 238:3,5,12 239:1,2,9,20 240:3,10,14,19 241:2,10 242: 10 246:10 247:16,19,22,22 248:2,18 250:3,5,6,8 251:3 254:10 255:1,19 256:6,22 258:3,4 266:1,21,21 269:13 270:12 271:8 274:1 276:6 278:13 279:20 282:17 285: 18 287:6 288:11 290:2,3 291: 2 292:3,7,8,15,16,17 294:4,7, 9 295:20 296:1,22 297:20 299:5 300:8,16 301:4,14,17, 17,18,18 302:11,18,21,22,22 303:13,17 304:10 305:2,6 306:11,16,16 308:10,12,14 309:12,14 311:6 312:14 314: 19,19 315:8,9,11,12,15,16 316:3,7,12,12,14,21,22 317: 16 318:5 319:1,11,12,12,13, 13,20 321:18 322:1 323:4 324:2,3,4,5,7 325:7,8,13,14, 15,15,17 326:15,20 327:17, 19 328:13 329:11 330:5,6,8, 12,13,13,17,18 331:1,2,2,3 332:17,20 333:5,11,17,20,22 334:7,14,21 335:9,15 336:14 338:9 339:12,15 340:16,19, 21 341:3,15,22 343:3,16 344: 5,20 345:11,15,21 346:9,9,10, 12,20 347:22 348:9 349:4,7 350:1,10,10,11 352:9,10,18 353:4,7,8,10,14,16,18 354:10 355:10,12 356:8 357:7,8,15, 20 358:19 359:4,5,9,12,18,19 360:13,17 361:3,10,10,20 364:4,16,22 365:13 366:6,22 367:10 369:17 370:8,15,18 371:2,6 372:9,17 373:3 374: 7 375:8,12,20 376:11,18 377: 16,21 379:4,11,15,17 381:3, 15,18,19,19 382:9 383:2 it's ^[20] 35:13 127:22 137:11 152:5 182:9 183:11 202:1 209:13 210:15,20,21 319:16, 17 326:19 329:19 337:10 339:8,9 342:5,20 item ^[8] 28:11,12 336:2,3,6 383:7,11 385:2 items ^[1] 31:8 iteration ^[1] 381:22 iterative ^[1] 156:21 its ^[38] 5:19 9:17 11:3 32:2 42: 7 49:17 50:1 52:21 53:21 88: 20 95:17 152:3 159:8,20 168: 12 183:10 190:1 196:18,19 199:9 203:6 212:6 223:5,6 224:10 230:3,12 231:21 232: 9 244:12 246:12 255:2 295: 22 298:9 330:5 335:20 341:3</p>	<p>385:11 itself ^[14] 16:17 59:3 105:1,2, 19 146:22 201:5,9 265:1 279: 2 291:2 298:13 304:9 316:2 ITT ^[3] 170:18,21 173:18 ITT-LOCF ^[3] 83:5,10 87:1 ITT-LOCF ^[3] 80:1,21 81:8 IV ^[2] 334:11 377:7 IWQOL-Lite ^[1] 91:6 <hr/> J <hr/> J ^[2] 2:2 3:3 Jack ^[1] 49:5 Jackson ^[1] 7:5 January ^[1] 299:13 jerking ^[1] 305:1 Jessica ^[4] 2:8 7:22 364:12, 13 jibe ^[2] 171:3,18 job ^[4] 236:3 329:19 372:2 380:19 joint ^[1] 161:6 Jones ^[3] 327:7,11,12 Journal ^[2] 25:6 288:16 judgements ^[1] 372:11 Judith ^[1] 327:12 Judy ^[1] 327:6 Jules ^[4] 2:15 6:20 328:22 329:14 July ^[1] 14:4 jump ^[1] 352:12 jumping ^[1] 337:4 June ^[5] 1:7 43:15 44:4 144:9, 10 just ^[135] 15:14 18:17 22:10, 18 24:1,18 26:5 27:8,18 28:6, 21 29:10,22 30:3 33:1 34:5 41:3 42:11 43:9 44:17,18 55: 4 57:2,18 58:14 66:6 79:15 80:16 111:8 114:2 132:22,22 133:4 141:14 142:15 144:2,6 149:6,20 152:20 154:1,7 155: 20 161:8 165:13 174:4 178: 16 181:16 182:6 185:1 210: 14 219:12 222:7,15 223:20 225:1,2,17 230:10,21 234:21 235:15,18,22 236:6 238:22 240:13 242:10 246:20 249:5 250:15 251:3 262:16 265:22 275:7 276:19 286:3 287:5 293:20 294:2,15 299:3,17 300:2 301:2 303:3 304:12 306:16 307:12 310:20 312:8, 15 313:12,19 315:9,17 318:6, 22 321:13 323:22 326:15 328:17 329:8 330:19 331:22 333:22 338:6 339:3,18 340:1 343:22 347:1,6 349:17 354:6 356:10 358:16 360:9 364:19 365:8 368:6 369:11,13,14 370:1,6,12 375:14,17 376:19 377:20 378:15 380:12,14 385:5 <hr/> K <hr/> Karen ^[13] 2:24 3:28 6:14 11: 18 185:4,15 215:14 219:16 221:1 222:12 246:20 250:11</p>	<p>323:13 Karen's ^[1] 222:8 Katherine ^[5] 2:7 7:20 362:3, 4 364:11 keep ^[13] 10:15 12:5 33:14 106:10 153:19 198:15 241: 16 242:19 253:18,20 280:2 298:4 363:22 keeps ^[1] 315:12 Kelly ^[5] 3:10 9:10 11:6 13:19 282:22 Ken ^[5] 8:4 37:14 49:3 367:18 382:8 Kenneth ^[2] 2:5 3:15 kept ^[5] 97:4 132:16 184:8 241:20 242:1 ketamine ^[1] 197:18 key ^[17] 12:3 33:8 39:18 51:15 55:9 61:14 72:7 142:7 146:3, 13,14,15 147:9 156:17 203: 15 211:4 250:9 keys ^[1] 147:21 kg ^[1] 176:14 kg/m2 ^[3] 38:15,15 47:4 kill ^[2] 22:16 24:9 kilogram ^[1] 176:13 kilos ^[1] 174:18 kinase ^[1] 195:20 kinases ^[1] 195:21 kind ^[15] 28:18 35:1,16 178: 20 238:9,17 306:19 315:10 319:10 320:10 329:16 372:8, 11 374:19 375:1 kinds ^[3] 226:7 229:2 335:3 Kingdom ^[1] 293:13 kit ^[4] 152:10,11,17,18 knew ^[3] 19:17 371:1 372:6 knocking ^[1] 233:8 knockout ^[1] 233:6 know ^[83] 10:21 13:21 17:12 19:3 20:3,17,19 22:7,18,20 28:21 31:18 34:10,17 35:10, 13 36:1 43:20 153:1,12 164: 22 168:16 177:1 180:16 182: 7 183:17,19 216:6 218:12 236:2 240:10,16 242:13 258: 6 287:2,11 292:7 296:12 303: 13,17 307:7,10,12 308:8,11, 13 309:17 314:12 316:14 317:18 319:5 321:11,17,18, 19 324:1,9 329:19 332:6,14 334:12 335:18 336:11 337:1 345:9 348:4 349:2,21 351:2 353:16 355:15,15 357:2 362: 22 364:9 370:3 371:20,21 373:7,20 375:18 378:10 380: 16 knowing ^[2] 27:21 321:22 knowledge ^[2] 138:4 298:2 known ^[7] 44:3 61:7 163:22 223:6 243:12 272:16 298:9 knows ^[3] 18:22 31:20 301: 12 Kreisberg ^[17] 2:16 7:6,6 218: 11,12,12 300:5 342:22 343:1 344:2 345:9,21 347:18 349: 14 380:16 384:2,3</p>
--	--	---	--

Kreisberg's ^[1] 385:9 Kresiberg ^[1] 347:17 <hr/> L I ^[1] 275:19 label ^[4] 44:1 138:3 182:9 231:9 labeled ^[1] 25:12 labeling ^[10] 17:15 20:18 138: 15 168:2 182:11 183:2,20 184:2,6 323:20 labels ^[2] 21:15 26:6 Laboratories ^[1] 9:18 Laboratory ^[2] 7:5 289:16 lack ^[14] 16:11,16 175:17 196: 13 232:17 234:19 268:18,19 298:21 301:6,14 334:22 370: 21 381:14 ladies ^[2] 49:15 93:10 language ^[7] 16:17 19:18,21 152:3 182:8 184:5 302:18 languages ^[1] 32:6 lap ^[3] 162:9,16,20 large ^[14] 32:3 87:15 111:16 132:8 134:10 173:4 256:19 265:6 279:10 284:8 315:13 325:3 342:4 363:8 largely ^[3] 114:14 121:17 354: 4 larger ^[7] 135:20 215:19 279: 14 290:15,17 328:3 343:7 largest ^[1] 257:15 laser ^[1] 237:18 last ^[20] 14:16,16 35:6 71:19 119:4 144:15 172:18,21 173: 15 225:17 234:9 248:16 254: 18,21 294:3,17 323:1 338:4 358:20 359:7 lastly ^[7] 140:13,17 141:18 142:11 144:2 147:5 191:12 late ^[2] 132:15 181:13 later ^[20] 11:10 17:19 40:14 42:5 44:6,15 45:1 55:12 65:9 73:21 98:12 118:16 128:17 134:5 181:18 182:19 242:11 266:10,13 289:6 latter ^[2] 105:16 124:14 launch ^[5] 143:15 151:9 155: 4,9 156:12 launched ^[3] 44:5 142:21 144:10 layers ^[1] 302:11 LCDR ^[5] 2:3 3:6 7:2 8:15 250:15 LDL ^[4] 78:13 83:22 253:13 298:22 lead ^[10] 24:6 29:13 71:13 194:14 195:22 201:4 288:19 289:3 298:10 330:9 lead-in ^[1] 130:17 lead-out ^[1] 130:18 Leader ^[1] 324:16 leading ^[6] 29:12,17 80:11 159:17 192:20 200:1 leads ^[5] 17:3 26:19 65:15 192:2 331:10 leaflet ^[1] 44:2 lean ^[4] 61:18 66:1 363:18,20	learn ^[1] 334:2 Learned ^[2] 155:7 298:4 learning ^[2] 190:22 331:13 least ^[19] 13:6 23:19 47:5 79: 6 98:15 151:8 252:11,13 279: 7 296:4 320:1 324:10 329:1 334:1 341:16 365:4,5 373:19 383:18 leave ^[4] 325:15 329:17 335: 18 350:2 lecture ^[1] 246:19 led ^[3] 98:5 125:20 326:17 Lee ^[1] 308:4 left ^[12] 52:22 54:2 61:15 64:8 83:4 87:6 90:11 103:21 106: 3 232:21 358:4 367:2 leg ^[1] 263:17 legal ^[1] 335:4 legs ^[1] 301:18 length ^[1] 315:20 leptin ^[3] 65:14,14 66:2 lesions ^[6] 216:18,19 217:3, 17 218:1,7 less ^[42] 18:18 29:20 55:3 81: 2,6 104:1 113:2 115:11 123: 9 124:21 145:12 162:17 176: 21 178:22 189:9 192:17 206: 1,20,22 209:3,13 216:2 227: 10 236:7 248:4 253:15 282:9 287:12 290:22 309:11 316:4, 16 326:13 336:18 339:9 340: 18 348:1 354:16 363:15 364: 5 366:11 374:9 lesson ^[1] 121:9 Lessons ^[1] 155:7 Let ^[14] 12:6 43:9 89:14 144:6 159:14 175:9 185:1 217:8 247:8 262:16 301:7 312:8 318:19 345:18 let's ^[10] 61:5 82:20 85:13 89: 1 90:8 142:17 151:5 169:3 347:17 376:11 lethality ^[3] 17:1 31:2,4 lethargy ^[3] 264:8 305:21 342:9 letter ^[3] 45:7,12 287:7 letting ^[1] 329:16 level ^[30] 12:12 54:9,20 55:3 56:4 64:11 102:17 103:9 108: 22 194:7,7,8,9,11 195:16 205: 12 208:4,8 247:12 248:9,14, 22 249:20 329:2 336:6 340:8 361:1 362:1 385:17,17 levels ^[16] 52:13 61:15,20 62: 4,16 63:8 92:6 191:16,18 194:6 213:12 220:13 253:8, 13 273:21 297:8 life ^[31] 24:17,21 70:12 72:13 90:20 91:8,10 92:14,15 113: 16 161:7 165:7 168:14 170: 18,20 171:9 172:9,18 173:2,6, 11,21 177:21 178:5 240:4 244:7,8,18 357:21,22 358:22 life-long ^[1] 257:4 life-threatening ^[1] 181:9 lifestyle ^[5] 72:19 86:20 146: 21 151:16 245:10	Lifetime ^[10] 33:6 204:18 209: 7,18 217:14,14 240:1,15 364: 15,21 ligand ^[3] 196:3 197:14 203:1 ligands ^[2] 50:17 187:20 light ^[5] 88:20 98:9 138:7,17 350:12 like ^[109] 5:20 6:1 9:1,10 10: 16,18 13:13 14:7 16:2 20:16 26:1 30:5 33:17 34:8 35:12 42:11 44:17 49:15 50:21 53: 14 55:5 69:1 90:19 93:2 120: 22 128:9 132:11 134:14 135: 9 137:8 140:3 148:22 149:1 154:8 155:20 158:13,15 161: 20 165:12 167:19 170:13 171:4 174:3 183:6 184:17 188:7 232:4 234:21 237:22 239:12 240:17,18 241:3,18 242:10 249:5 250:13 284:1 294:12 299:3 307:22 308:14 309:17 314:6 316:13 317:11 318:20 320:13 324:3,4,11 325:14 327:1 340:4 345:4 347:6 348:16 350:8 353:3,14, 16,21 355:10,12 356:20 357: 2 358:13 360:17 363:15 364: 17 368:17 369:10 372:18,20, 22 373:9,20 374:16 375:3,17 377:16,17,21 378:12 380:18 381:19 385:6,9,20 likelihood ^[1] 106:1 likely ^[14] 57:10 106:19 131:7, 8,13 132:3 133:2,15,19 170:3 230:21 277:2 314:5 320:11 likens ^[1] 166:6 Likewise ^[2] 205:21 223:10 limb ^[1] 305:2 limbic ^[2] 61:9 67:7 limit ^[2] 114:9 242:9 limitations ^[1] 27:2 limited ^[13] 26:22 58:19 93: 21 168:8 183:22 196:13 214: 2 230:16 231:18 245:2 317: 21 319:14 366:12 limits ^[1] 229:19 Linda ^[1] 49:4 line ^[10] 56:5 89:21,21 105:3 106:10,15,17 114:17 303:20 326:18 linear ^[4] 89:10,17 90:8 331: 21 lines ^[5] 90:3,12,15 291:14,14 link ^[3] 27:14 136:5 196:8 linked ^[1] 193:3 lipid ^[4] 51:2 65:5 244:9 255: 12 Lipids ^[3] 39:7 66:18 300:16 lipophilic ^[1] 188:3 list ^[6] 141:14 153:2 262:17 263:19 374:19 375:1 listed ^[8] 53:6 97:12 128:7 136:4 182:14 188:19 216:12 306:10 listing ^[1] 276:20 literally ^[2] 328:14 365:13 literature ^[6] 175:5 193:19	194:20 195:3 196:17 232:22 litter ^[1] 231:6 little ^[26] 36:11 58:16 61:5 86: 12 108:19 120:4 126:12 134: 4 144:6 150:5 161:17 175:14 176:17 237:13 242:11 247:9 265:14 285:18 286:7 300:14 339:15 347:2 352:6 353:21 366:11 378:15 live ^[1] 242:18 lived ^[1] 242:15 liver ^[7] 52:10 67:11 189:15 224:19 225:6 231:11 244:10 living ^[2] 156:22 371:6 locally ^[1] 188:9 located ^[4] 189:7,12 224:22 257:10 location ^[1] 278:12 LOCF ^[2] 172:7,17 lock ^[1] 55:15 lodging ^[1] 223:9 log ^[1] 34:10 logical ^[1] 164:9 long ^[9] 42:20 153:2 241:16 245:14 257:22 337:1 357:3 370:11 378:16 long-term ^[27] 47:9 66:14 73: 14 79:10 91:16 146:19 216: 21 217:6 218:14 232:4,6,10, 15 233:17 244:14 309:4 322: 8 338:17 357:3 360:14 361: 11 364:17 365:1,2,3,13,16 longer ^[6] 64:13 208:19 233:3 305:17 361:12,16 longer-term ^[1] 368:5 look ^[54] 14:10 19:20 29:22 61:6 81:21 103:13 105:12,21 106:5 112:20 126:17 148:16, 22 149:1 150:20 154:8 177:3 178:5 196:3 197:14,14 199:1 201:20 202:5,11 205:14 206: 5,6,19 209:2 210:11,16,17 218:8 220:7 248:6 249:20 279:13 294:11 296:22 305: 10 316:14 324:9 326:16 330: 19 346:8 359:10 360:17 361: 3 364:15 366:19 371:3,14 385:13 looked ^[20] 28:14,15 58:21 71:19 179:8,15 235:4 265:6 279:3 294:12 300:14 303:10 304:18,19 308:14 318:1,3,14 345:19 349:2 looking ^[33] 25:11 58:1 62:18 64:14 65:11 86:5 114:6 117: 18 143:21 152:13 154:18 169:11 183:18 208:16 222:9 234:1 238:4 247:16 248:8 257:4 263:7 278:3,11 286:3 294:20 313:12 315:9,17 358: 4 381:20 382:15 385:5,16 looks ^[11] 291:10 324:2,4 325: 13 331:2 341:15 343:17 344: 9 355:10,12 366:14 losartan ^[1] 54:12 lose ^[18] 71:4 162:15 171:22 172:1 174:4,5,17,18 234:4
--	---	---	---

<p>236:17 321:16 332:21 333:1, 3,7 349:22 361:20,21 losing [3] 71:10 236:16 258:7 loss [133] 63:10,11 69:16 71:4, 6,11,15,16 72:6,9,16,20 74:5, 8 75:13,16 79:14 80:4,10,11, 18,20 81:1,5,12,14,17 82:1 84:11,22 87:20 89:3,8,12,16, 19 90:1,6,13,16 92:13 103:6 111:22 118:17 125:9,17 136: 13 137:12 148:5 160:13 161: 3 162:15,17 163:10,12,14,15, 21 165:4,5 169:4,7 171:21 172:2 175:8,18 176:5,7,11,15, 19,22 177:3,8,15 182:9 190:5 212:8,21 213:19 232:12 233: 13 234:12 238:1,16 242:4 244:16 252:10,11,13 253:7, 16 262:20 264:10 278:13 279:2 291:2,5,17 297:6 298: 12,14 301:17 307:18 308:22 326:10 330:9,12,14 331:10, 20 332:3,11 337:4 343:15,16 344:10 345:11,20 348:9,20 359:21 360:1,10,15,16 361: 15 364:4,6 370:20 382:17,18, 20 losses [1] 244:20 lost [13] 63:16,22 75:2 80:15 86:12 163:7 176:14,17 302: 16 326:5,13 350:5,6 lot [37] 5:13 18:11,19 27:11 29:11 33:2,11 46:21,22 47: 10 108:18 171:22 225:8 236: 20 238:5 240:5,6,19 241:2,15 243:4 298:3 302:16 306:18 314:5 315:6 321:12 330:10 347:19 353:13 362:19,22 363:11 377:5 378:12 379:2 385:4 lots [1] 335:13 Lou [1] 37:22 Louis [2] 3:24 157:20 love [1] 378:10 low [20] 29:19 53:2,2,10 62:21 70:14 82:22 122:12 162:11 191:7 207:2 209:19,22 228: 17 257:13 293:5 325:7 343:4 364:1,2 lower [12] 54:22 73:22 78:12 82:15 110:21 114:9 176:18 208:19 242:12 325:10 340: 13 355:13 lowest [2] 205:11,14 luck [1] 25:1 lump [1] 339:5 lumped [1] 238:17 lumping [3] 345:1 347:2,9 lunch [2] 11:21 185:7 lunge [1] 334:4 lutea [1] 231:3 lymphocytes [1] 62:18 lymphoma [2] 231:12,12 Lynn [6] 4:6 235:9,10,11 243: 6 352:21</p>	<p>M.D. [24] 2:2,5,6,12,13,14,15, 16,17,18,20,22,23,25,26 3:3, 8,15,18,20,24 4:3,15 223:22 MAA [1] 43:13 Mackie [11] 3:15 37:14 42:5 49:3,6,10,12 68:22 88:14 326:2,11 Mackie's [2] 197:8 198:16 macrovascular [1] 169:16 made [17] 8:17 19:9 26:7,10 37:13 51:2 63:14 172:10 190: 2 240:22 306:1 313:3 332:10 343:9 347:16 350:11,19 magic-bullet [1] 224:9 magical [1] 382:19 magnitude [1] 290:4 main [4] 123:7 140:7 158:16 322:11 mainly [3] 180:6 310:10 368: 10 maintain [4] 162:15 252:13 259:21 332:10 maintained [8] 84:10,21 92:7 97:1,2 125:4 155:20 174:10 maintaining [1] 96:7 maintenance [3] 225:14 284: 9 322:9 major [10] 69:18 113:20 165: 11 183:20 184:4 205:2 220:2 244:14 282:7 339:20 majority [8] 106:5 161:14 173:4 271:18 283:17 303:16 304:22 330:17 make [39] 20:20 25:9 35:4 113:5 132:4,5 134:15 149:19 151:9 154:5 155:17 156:13 158:16 161:14 178:1 183:6 235:15 238:15 239:9 240:20 241:7 243:12 246:12 249:6 250:15 289:10 295:17 316: 13 319:2 324:4 325:14,17 333:16 335:12 349:8 359:9 371:22 372:11 377:3 makes [9] 9:9 164:15 166:12 237:8 240:20 296:5 339:9 344:20 353:19 makeup [1] 228:2 making [7] 10:19 87:14 149:7 222:18 235:21 273:20 313:5 mal [7] 130:3,3 319:13,14,15, 17,18 male [5] 17:17 209:17 286:22 287:1,10 males [3] 278:22 352:16,17 man [4] 70:6 117:17 118:7,22 manage [1] 160:17 manageable [3] 122:10 159: 9 167:11 managed [1] 334:18 Management [18] 3:21 11:3, 4,16 13:4 37:20 46:2 48:20 140:4 145:14 159:13 164:9 169:1 214:11 327:22 334:8 335:1 383:17 managing [3] 160:10 168:9 170:1 mandated [1] 19:3</p>	<p>mandates [1] 15:20 manipulated [1] 163:1 manipulates [1] 366:1 Mann [1] 29:13 Mann's [1] 23:13 manner [4] 84:2 193:21 245: 21 373:8 manual [1] 144:2 manuals [1] 34:19 many [49] 14:9,9 17:12 28:17 31:17 48:13,14 52:12 54:10 57:20 59:7,10 70:20 71:3,13 74:5 134:9 136:3 149:11 158: 18 159:20 169:20 196:5 207: 12 227:12 231:22 236:17 239:2,3,3 240:2,4 257:2 265: 20 268:18 271:11 273:7 279: 15 296:12 297:21 305:19 306:14 314:12 341:7 349:22 362:5 363:12 367:1 370:1 map [2] 140:7 195:21 March [5] 94:10 97:14 259:1 293:11 311:15 marginal [6] 208:1,12 247:16, 19 248:12 249:21 margins [2] 215:4 270:8 Marie [1] 322:3 marital [1] 118:17 marked [1] 64:17 markers [3] 161:7 164:21 165:1 market [10] 42:7 161:15 240: 11 296:14,16,19 298:8 337: 12 352:19 380:19 marketed [2] 40:15 43:12 marketing [3] 43:13 314:14 383:2 marketplace [1] 155:5 marry [1] 236:7 marvelous [1] 337:6 Mary [2] 2:22 6:8 mass [1] 13:5 massive [2] 334:4 364:18 match [1] 315:16 matched [1] 62:2 matching [1] 177:14 Material [9] 152:2 155:7 170: 19 250:21 301:5,5,6 308:13 312:15 maternal [1] 323:18 matter [3] 89:6 133:7 202:20 matters [1] 89:7 Mattson [3] 320:4,6,7 maximal [1] 248:9 maximally [1] 54:5 maximum [1] 163:10 may [86] 10:6 13:20 17:7,8 21: 12 22:13,14,16,21 27:18 28:2 31:18 43:20 53:19 55:20 68: 10 71:19 81:2 89:5 103:13 117:9 118:8 119:16 138:1,3 153:2,12,12 168:14 180:4 181:17 182:16 191:10 195:4 199:12 201:6 214:16 223:5,8 228:17,19 233:7 251:22 255: 22 267:8 274:11 278:14 288: 4,12 291:5 293:5 298:12 299:</p>	<p>13 304:8 306:15,16 307:11 312:19 326:16 332:14 347:8 350:16,21 351:9,10,10 356: 19 358:1,21 359:12,14 361: 18 362:10 363:9,16,21 364:5, 7 366:11,17 367:10 368:10, 10 369:19 379:19 380:7 Maybe [7] 172:12 177:1 310:2 332:9 355:4,14 359:16 McAffee [4] 4:6 235:9,11,12 MD [1] 1:11 me [43] 6:5 12:6 35:8 43:9 89: 14 138:10 144:6 159:14 175: 9 185:1 217:8 221:2 239:9, 20 242:15 247:8 262:16 301: 2,7 312:8 318:19 319:8 327: 6 329:16 330:13 331:1 338:7 340:19 343:17 345:18 348: 22 353:19 356:5,8 357:8,13 358:8,19 365:9 368:2 373:14 378:20 379:5 mean [40] 15:11 22:4 23:18 27:8,9 33:13 80:17 98:8 228: 6,13 238:9 239:17 252:10,11 255:17 289:13 291:12,16,21, 21 301:14,17,17,18,19 304:2 307:21 308:5 319:17 339:16, 17 342:2,6,9 358:4 359:8 360:1 361:19 376:3 378:21 meaning [4] 17:4 28:19 75: 22 252:1 meaningful [4] 19:21 32:15 271:15 326:21 means [10] 31:21 232:13 241: 12 243:4 247:12 262:17 301: 13 302:3 349:11 374:18 meant [4] 261:22 306:3,14 339:16 measure [9] 56:13 63:18 146: 1 154:10,10 168:5 325:15 353:1 378:1 measured [4] 174:7 321:18 360:12,13 measurement [3] 32:10 92: 14 306:3 measurements [2] 254:11 305:22 measures [8] 31:16 35:16 141:9,12 142:1 177:21 259: 15 260:19 Measuring [3] 254:19 372:15 378:5 Mechanism [25] 3:14 11:15 37:14 48:13 49:8,11,16 50:1 65:12 67:4 158:22 183:10 186:6 194:13 198:2,5,11 203: 6,10 213:18 215:10 326:14 331:5 348:20 370:19 mechanisms [9] 43:7 59:11, 12 63:12 81:4 197:22 198:12 242:3 245:7 Mechoulam [1] 50:13 MedDRA [1] 276:7 media [4] 5:16,18 64:14 184: 17 median [2] 104:8 289:13 mediate [1] 207:11</p>
--	---	---	---

M

M [4] 2:7 4:3,10 223:18

<p>mediated ^[9] 59:8,10 60:4,6 63:19 64:5 193:9 224:10 326:17</p> <p>mediator ^[1] 59:16</p> <p>mediators ^[2] 188:14 193:21</p> <p>Medical ^[35] 3:16 4:7 6:12,18 7:1 12:2 37:1,16 69:4,7,11 72:1,2 74:9 101:5 102:21 103:18 104:15 119:12 129:8 138:8 139:3 141:10 157:21 159:14 169:19 235:9 243:2 266:4 275:11,13 276:6 279:12 282:15 357:18</p> <p>medically ^[7] 122:9 123:16 125:3,11 181:7 244:17 346:5</p> <p>medication ^[16] 18:4 21:11 27:16 32:13 141:15 142:6 150:13,14 153:11 167:9 229:6 257:4,4 348:2,7 368:1</p> <p>medications ^[9] 161:9,21 165:13 166:21,22 245:20,21 356:6 363:6</p> <p>Medicine ^[8] 6:18 7:9 16:10 48:15 69:2 157:21 229:10 288:17</p> <p>MedRA ^[3] 103:8 123:4 130:1</p> <p>meds ^[1] 21:12</p> <p>medulla ^[1] 191:4</p> <p>meeing ^[1] 385:20</p> <p>meet ^[5] 128:13 174:19 252:17 309:1 336:16</p> <p>Meeting ^[21] 5:5,13,18 8:18, 19,22 9:2,12 10:17 12:10 13:15,16 14:16,17 34:16 177:7 222:20 223:10 250:22 336:18 385:21</p> <p>meetings ^[1] 376:21</p> <p>Melanie ^[6] 2:11 7:10 323:3 352:1 354:2 378:9</p> <p>Melanie ^[1] 351:22</p> <p>member ^[1] 369:10</p> <p>Members ^[18] 2:4,10 5:10,15 8:20 10:19 13:14,21 36:19 49:14 69:9 93:9 139:5 148:16 158:12 184:18 251:10 299:18</p> <p>membrane ^[3] 51:2 188:4,16</p> <p>membranes ^[1] 56:9</p> <p>memo ^[1] 309:2</p> <p>memory ^[14] 125:9,9,17 136:13 187:16 191:1 194:10 226:1 261:4 264:6,9 305:19 342:2,7</p> <p>men ^[3] 300:8,10 310:8</p> <p>Meniere's ^[1] 303:15</p> <p>meningioma ^[1] 341:13</p> <p>Mental ^[5] 7:15 91:1 178:7 179:6 357:22</p> <p>mention ^[5] 267:15 299:3 302:2 314:19 316:20</p> <p>mentioned ^[17] 15:10 41:20 43:11 53:12 147:21 151:19 180:11 182:8 231:14 239:14 241:13 316:22 324:1 334:5 356:17 367:20 370:3</p> <p>merely ^[2] 54:4 57:15</p> <p>Meridia ^[2] 182:9 184:6</p>	<p>merit ^[1] 244:2</p> <p>message ^[2] 55:16 155:17</p> <p>messages ^[3] 146:13,15 147:9</p> <p>met ^[4] 79:15 124:19 177:2 308:22</p> <p>Meta-analyses ^[3] 259:6,19 260:7</p> <p>meta-analysis ^[8] 114:3,4 116:11 260:3,3 264:17 285:12 292:19</p> <p>meta-analytic ^[1] 111:10</p> <p>Metabolic ^[23] 5:4 13:22 47:5 63:12 66:17 67:15 68:11,13 69:15 78:10,11 82:20 89:2, 11,15,18 92:12 168:12 185:16 186:21 312:11 348:15 382:15</p> <p>Metabolic/Endocrine ^[1] 224:5</p> <p>Metabolism ^[11] 6:9,11,16 65:6 66:18 68:1 93:3,14 187:4 188:17 189:19</p> <p>metabolized ^[1] 42:22</p> <p>metformin ^[8] 39:13 46:18 76:13 85:18 86:18 87:8 91:21 99:19</p> <p>method ^[9] 89:13 111:8 114:5,5 116:12 169:21 230:7 367:12 368:13</p> <p>methodologic ^[1] 230:6</p> <p>methodological ^[1] 367:13</p> <p>methodology ^[9] 89:10 101:14 109:8,14 283:2 284:2 302:8 304:14 378:3</p> <p>methods ^[1] 305:4</p> <p>metoprolol ^[1] 54:11</p> <p>mg ^[112] 39:21 42:8 74:21 75:10,14,16,20 76:17 79:11,16 80:4,13 81:14 82:4,12 83:8, 15 84:21 86:5,21 91:9 92:4,8 94:17,18 96:7,7,8,11,12,14 97:17 111:13,17,18,20 112:2, 4,7,8 113:20 114:22,22 115:8, 11,12,13,15,21,22 116:3,4,6 118:22 119:1 121:20 122:4 124:10 126:13,13,17,17,19 131:1,1 132:15,18 133:5,14 134:6 175:13 176:16 177:11, 12,15 179:8 205:18 213:13 226:20 247:18,22 248:15 252:21 256:18 257:18,18 259:13 267:18,22 270:2 277:1 281:6,20 284:13 285:3,14 286:6,21 287:1,2 292:22 309:10 311:6,20 316:3,12 338:21 339:4,6,7,8 344:10</p> <p>mg/day ^[5] 63:15 208:8 211:2, 17 213:6</p> <p>mg/kg ^[7] 208:4 209:1,10 210:8,8 247:20 248:2</p> <p>mg/kg/day ^[2] 209:5,8</p> <p>Miami ^[1] 303:7</p> <p>mice ^[10] 63:14,21 204:12 216:2 233:6,6,13 269:22 270:3 326:3</p> <p>Michael ^[10] 2:9 127:4,6 315:</p>	<p>4 322:21 359:2,3 372:12 378:17 380:11</p> <p>Michigan ^[1] 7:1</p> <p>micromolar ^[3] 53:15 56:16 197:19</p> <p>microphone ^[2] 172:13 327:7</p> <p>microvascular ^[1] 169:16</p> <p>mid-40s ^[1] 77:14</p> <p>mid-50s ^[2] 77:16 86:9</p> <p>mid-dose ^[1] 209:19</p> <p>mid-to-late ^[1] 183:8</p> <p>middle ^[2] 61:18 242:16</p> <p>middle-aged ^[3] 255:7 323:6 365:8</p> <p>might ^[24] 13:10 51:12 134:3 217:6 218:9 228:21 230:2 233:2,22 288:8,19 303:2 307:20 337:6 343:6,12 349:1 354:16 355:4 356:8 361:17 367:7 376:9 378:13</p> <p>migraine ^[1] 167:1</p> <p>Mike ^[3] 7:18 338:2 347:13</p> <p>mild ^[2] 76:19 100:2</p> <p>MILL ^[1] 386:1</p> <p>Miller ^[6] 2:3 3:6 7:2,2 8:15 250:15</p> <p>million ^[3] 33:9 70:4 161:1</p> <p>millions ^[1] 365:14</p> <p>mind ^[14] 33:14 184:8 198:15 242:20 253:19,20 280:2,4 298:4 336:5 338:14 340:2 343:20,22</p> <p>mindful ^[4] 143:6 149:11 150:18 154:14</p> <p>mine ^[1] 381:16</p> <p>mini-blinds ^[1] 18:7</p> <p>Mini-Mental ^[2] 306:1 307:8</p> <p>Minimization ^[4] 44:16,19 140:17 145:18</p> <p>minimize ^[6] 145:15 165:15 351:14 362:10 369:20 382:9</p> <p>minimizing ^[3] 168:5,19 172:8</p> <p>minimum ^[3] 10:15 30:22 31:9</p> <p>mining ^[1] 314:19</p> <p>minor ^[5] 19:10 174:2 351:9, 10,10</p> <p>minute ^[2] 149:6 293:21</p> <p>minutes ^[7] 29:20 34:18 184:10 232:21 258:11 284:2 307:9</p> <p>misclassification ^[1] 26:19</p> <p>misleading ^[2] 28:20 230:20</p> <p>misperceptions ^[1] 24:5</p> <p>miss ^[1] 129:19</p> <p>missed ^[3] 17:7 20:21 25:9</p> <p>missing ^[3] 233:6 250:17 359:1</p> <p>misunderstood ^[1] 335:8</p> <p>mix ^[1] 219:22</p> <p>mixed ^[1] 24:7</p> <p>mode ^[1] 67:14</p> <p>model ^[10] 66:21 68:13 89:14 90:9 164:3 210:9,19,21 225:18 278:7</p>	<p>models ^[15] 57:20 60:19 200:16 203:4,8,9 206:13 215:22 219:5,6,9 222:10 235:1 247:1 267:5</p> <p>moderate ^[2] 266:10,11</p> <p>moderately ^[2] 11:6 253:3</p> <p>moderator ^[1] 37:2</p> <p>modern ^[1] 50:9</p> <p>modest ^[9] 42:19 43:2 72:5 74:8 107:16 135:13 234:13 245:4 348:9</p> <p>modification ^[1] 307:16</p> <p>modifications ^[2] 146:9 156:13</p> <p>modified ^[1] 148:10</p> <p>modulate ^[2] 192:9 193:11</p> <p>modulates ^[1] 192:4</p> <p>modulation ^[7] 187:10,12 194:14 198:6 201:21 202:6 225:21</p> <p>modulator ^[1] 164:1</p> <p>modulators ^[1] 273:13</p> <p>modulatory ^[4] 186:16 191:21 200:1,18</p> <p>module ^[1] 196:20</p> <p>molecular ^[2] 194:7 195:16</p> <p>molecules ^[2] 188:3 193:19</p> <p>moment ^[6] 15:14 27:1 110:20 177:21 299:17 301:2</p> <p>moments ^[3] 139:15 141:15 142:15</p> <p>Monday ^[2] 380:22 381:1</p> <p>money ^[6] 236:20 240:6,8,12, 18 377:5</p> <p>monitor ^[6] 101:16 120:18 151:2 152:13 153:20 371:7</p> <p>monitored ^[3] 100:18 136:22 380:5</p> <p>monitoring ^[9] 28:1 29:8 30:7 31:15 100:19 138:15 167:16 168:3,22</p> <p>monkey ^[8] 204:15,16 205:22 208:21 209:12 212:21 218:21 247:14</p> <p>monkeys ^[4] 204:13 205:18 270:1,4</p> <p>monotherapy ^[1] 85:19</p> <p>month ^[5] 127:12 149:22 154:3 156:10 268:4</p> <p>month's ^[1] 240:9</p> <p>monthly ^[3] 152:14,15 155:17</p> <p>months ^[25] 66:8,10 88:4 117:19,21 118:3,12 130:18 148:8 163:7 176:1 204:16 209:4 217:9 239:2 240:14 266:13 270:16 275:1 289:6 299:10 309:6,7,22 330:18</p> <p>mood ^[37] 91:3 99:7 103:9,22 104:22 105:8,14 106:12 107:10 118:1 147:1 154:21 179:9, 16,21 266:7 273:19 274:6 275:14 276:14,16,20,21 277:19,20 279:13 280:3,8,11 282:4 290:14 293:16 297:13 317:22 318:2,7,18</p> <p>mood-disorder ^[1] 290:9</p> <p>moralistic ^[1] 56:5</p>
--	--	---	---

<p>morbidity [2] 298:14,20 more [157] 16:5 18:20 25:10 26:14 27:17,18 29:20 32:11, 14 40:5 50:20 53:7 57:12 58: 17 61:21 72:3 77:19 78:18 79:12,16 82:1 90:3 91:17 98: 11,16 99:13 100:16 104:1,21 105:4,5,15 106:19 107:5,8,14 108:10 109:1,10 110:14 122: 20 124:15 134:20 135:1,12 139:13 160:22 165:20 166:3 169:11 171:21 175:14,21 176:2,18,19 179:7 196:22 198:9,10 205:6,7 212:15 215: 6,18 216:2,4 226:22 228:22 230:3,21 234:13 235:3,4 236: 17 239:1 240:3 241:3 242:11 247:9 253:2 260:4 262:10 263:8 264:3 274:18 277:2 280:3,15 282:10 288:1,12 289:9,10 290:20,21 291:19 292:16 295:6 297:21 298:3 300:15 302:5,20 304:3,11 308:7 311:22 316:3 323:1 326:5,6,7,8 329:12 330:17 331:13 334:3 335:13 341:18 348:16 350:16 352:6 353:21 355:17,18,20 356:9 357:2,13 359:13 360:8,14 361:15,17, 19 364:6,16 365:8 367:4,7 368:17 372:5 373:20,22 374: 16,20 376:3,13,13,19 378:10, 13,15 379:4 385:4,13 Moreover [10] 65:4 72:9 96: 16,19 113:12 136:7 194:21 196:1 211:14 366:17 morning [30] 5:3 11:17 15:7 36:18 37:8 39:5 42:5 49:14 69:8 93:9,11 108:14 109:15 122:13 140:9,21 158:7 185: 14 187:3 198:16 203:5 221:4 222:9 226:2 232:16 234:1,22 345:22 381:1,1 morning's [2] 11:7 158:14 mortality [16] 66:9 162:19 163:9 205:15,20 206:9 210:9, 16 213:2 214:6 216:12,17 231:6 233:9 298:15,20 most [50] 12:3 16:12 19:22 21: 7 23:16 28:9 45:16 53:3 66: 17 71:4 77:17 78:11 96:1 98: 19 99:3 108:14 113:15 117:3 122:8 124:9 125:8,14 126:3 136:11 145:11 151:16 152: 21 156:8 165:10 183:16 186: 22 188:2 189:5,19 240:11 248:7 280:19 288:22 297:20 320:10 321:2,5 323:5 343:2 346:3,4 358:3,8 367:20 382: 21 mostly [4] 100:7 239:20 293: 12 340:18 mother [1] 18:5 motivated [1] 114:20 motivator [1] 326:16 motives [1] 24:8 motor [20] 124:1,18 187:16</p>	<p>194:9 201:14,21 206:9,19,20 212:4 213:3 214:6 225:22 260:16 261:4 262:4 263:3,8, 18 319:13 mouse [11] 204:17 205:21 208:20,22 210:9 212:21 231: 12 247:13,20 267:5 326:4 mouth [2] 24:2 320:13 move [14] 6:2 31:21 82:20 85: 13 89:1 100:21 115:14 129:5 246:18 247:2 303:21 340:4 372:18 374:14 movement [4] 190:18 200:5 202:5 320:14 moving [4] 62:1 72:1 74:14 198:9 MPH [4] 2:3,26 3:6 4:15 Mr [10] 36:18 49:14 69:8 93:9 139:5 140:1 158:12 170:7 181:12 376:10 MRI [5] 127:14 128:3,4,14 268: 4 mRNA [2] 64:11,20 MS [27] 7:10 59:20 127:16 128:12,15,19,21 129:3 235: 12 243:10 267:4,6,8,12,17,19 268:1,5,6,7,11,21 323:3 352: 1 354:1 378:10 384:6 much [44] 14:13 16:17 19:7 23:12 108:10 113:2 116:3 123:9 135:20 143:5 157:18 164:10 184:17 210:10 213: 22 227:6 232:20 236:14,16 240:22 241:9 243:1 245:7 303:19 305:16 312:14 319:8 321:9 326:22 327:11 329:22 332:5 333:5 343:6 347:16 351:21 354:2 360:21 362:2 369:17 376:3,22 381:11 385: 11 multi-factorial [1] 244:4 multi-site [1] 32:3 multifold [1] 31:14 multimeric [1] 195:8 multiple [35] 101:10 126:9,10 127:2,10,14,16,19,22 128:8 136:16 160:20 161:11 164: 14 168:10,13 186:11 196:1,8, 9 207:2 211:5,12 212:13 213: 8,12 218:1 226:6 238:20,22 239:4 270:7 340:19,20,22 multiple-sclerosis [1] 267:3 multiplicity [1] 59:22 muscle [7] 52:11 67:11 99:12 100:10 189:15 201:1 225:7 must [8] 54:20 60:22 162:22 252:8 253:20 290:2,4 369:4 mutation [3] 62:14,19,20 My [48] 14:15 15:15 16:1 18:5, 13 29:13 35:2 49:2,20 56:17 93:13 138:5,9 157:19 160:18 164:18 167:3,10 171:12,14, 19 172:10 179:10 186:2 187: 13 207:7 235:8 238:21,21 248:16 303:5,7,9 313:7 327: 11 331:16 340:8 349:18 351: 9 352:8 355:11 357:9 365:15,</p>	<p>20 369:12 374:5 377:20 381: 7 myocardial [2] 117:20 299: 11 myriad [3] 224:12 226:11 268: 16 myself [3] 37:13 246:1 335: 11 <hr/> N <hr/> N [9] 3:1,1 4:1,1 5:1 54:11 222: 1,1,1 N.D [1] 4:10 name [7] 21:9,9 56:18 93:13 153:15 303:5 327:11 names [3] 21:11 24:6 48:14 nanomolar [1] 57:4 narrative [2] 20:13 282:15 narratives [9] 21:3 22:13 109: 4 117:16 258:21 266:1 269:7 281:15 283:11 narrow [2] 212:6,11 narrower [1] 315:15 nasal [1] 183:4 National [1] 7:14 nationally [2] 32:4 34:17 natively [2] 56:6,8 natural [1] 340:22 naturally [1] 62:20 nature [11] 48:17 89:5 100:8 201:9 208:18 257:8 268:11 287:16 303:12 350:17 366:2 nausea [10] 98:20 126:6 166: 20 289:1,2,6,11 293:16 297: 18 301:17 nauseum [1] 376:21 NDA [8] 1:4 45:3 46:15 270: 21 271:3 282:12 310:16 369: 13 near [1] 199:4 nearly [2] 39:20 80:19 necessarily [5] 27:10 60:11 180:15 362:20 363:1 necessary [6] 32:20 34:9 45: 11 138:2 154:13 355:20 necessitated [1] 280:15 necessitating [1] 274:17 necessiting [1] 268:8 neck [1] 18:7 Need [41] 3:16 5:12 9:22 19: 15 31:1 37:16 69:5,7,11 105: 6 107:11 135:15 138:8,14 139:3 148:6 150:18 159:15 160:19 170:5 184:8 191:22 236:13 242:18 334:10,13 343:13,14 347:20 349:7,7 351:17 355:2 356:6 357:3 362:17 364:16 371:16 381:4, 4 385:8 needed [27] 19:18,19 21:20 30:10 73:14 104:4 181:4 205: 19 209:1 245:7 336:20 343: 17,18 344:6,7,11,15,16 345: 10,11,19 346:7,11 347:4,7,8 380:22 needing [1] 145:19 needn't [1] 330:4 needs [3] 169:19 340:15 375:</p>	<p>15 negative [4] 147:1 173:6 197: 7 198:6 neighborhood [1] 344:13 neither [2] 110:4 139:18 neocortex [1] 225:3 nerves [3] 52:4 67:8 261:6 nervous [36] 98:18 99:2 185: 21 186:8,11,18 189:6,12 190: 12 195:7 198:18 199:11,13, 16,19 202:21 203:20 205:2,4 206:8,15 207:9 211:21 212: 10,12,18 213:1,7,11,14,20 214:8 215:9 225:6 261:7 292: 10 nervous-system [1] 264:15 nervousness [1] 276:14 neural [2] 59:19 192:13 neuritis [2] 127:12 268:2 neurodegenerative [1] 267: 9 neuroleptics [2] 270:16,19 neurologic [15] 100:7 101:4, 9 124:1 125:19,21 126:2 130: 7 136:11 306:10 336:8 340: 17 344:3 346:3 368:6 neurological [31] 12:14 45: 20 251:20 258:13 260:5,14, 15,20 261:10,16 262:1 263: 20 264:13,22 265:4 266:3,14 268:12,17 270:14 297:16 306:19 329:5 343:10 346:1 347:10 351:8,14 361:5 369:2 374:8 neurologist [4] 127:5 149:14 301:12 374:22 Neurology [5] 7:1 48:20 303: 6 341:20 376:7 neuromodulatory [1] 203: 18 neuron [1] 192:9 neuronal [3] 191:16 207:18 269:18 neurons [3] 52:1 192:2 233: 14 neuropathic [1] 60:18 neuropathology [1] 217:1 neuropathy [1] 118:19 neuroprotection [1] 225:16 neuroprotective [3] 187:14 225:18 261:6 neuropsychiatric [3] 102:12 109:2 181:22 Neuroscience [2] 49:4 52:8 neurosis [2] 18:3 291:4 neurotransmission [7] 58:4, 9,12 192:11 193:14 194:12, 14 neurotransmitter [6] 58:5 193:8,9,13 194:15 231:20 neurotransmitters [3] 50:21 188:8 194:16 neutral [12] 42:3 54:3,7,12 55: 10,19 56:22 57:7,21 58:14,17 68:4 never [6] 15:20 25:1 292:3 301:12 339:19 376:12</p>
--	---	--	--

<p>New ^[21] 9:13 14:22 15:1 51:1 126:10 127:21 128:18 129:2 134:22 146:10 158:1 234:15 245:6 288:16 329:15 330:7 331:7 334:7,13 377:5 385:10 next ^[11] 53:19 66:6 68:17 75: 8 78:7 79:21 112:13 145:7 235:8 243:7 261:22 NIAID ^[1] 7:19 nice ^[3] 237:19 367:10 377:4 night ^[2] 242:16 338:5 NIH ^[3] 73:3 158:5 233:4 NIMH ^[1] 32:6 Nineteen ^[1] 131:11 NMDA ^[2] 194:18 197:19 NNH ^[1] 344:8 no ^[142] 8:21 12:20 13:8 16:13 18:21,21 19:11 20:20 24:4, 17 55:19 56:12 59:3 60:5 79: 10 83:21 90:3 100:1 102:8 104:10,11 106:3 110:16 112: 18 115:7 117:21 118:3,4 119: 4 120:7 123:16 124:19 125:1, 10 127:1,10 128:3,18 132:7, 16,16 133:7 134:7,11,22 136: 5,13,17,17 137:2 150:5 161: 15 163:7 171:12 177:22 182: 16 183:15,21 191:18 208:3 215:3 216:18,19 217:2,5 226: 10 230:17 232:3,10 245:16 247:11 248:13,21 249:17,19 253:12 254:3 262:16 263:15 266:4,14,17,18 270:3 271:12 278:17 279:6 284:13 285:15 305:12 307:5 314:15 330:9 332:10 335:21 336:2,3,6 337: 22 338:1,11 340:3 347:11,14, 14,14 351:20 353:22 354:1 355:21 358:14,15 361:10 362:1 364:9 365:17 367:16 369:6 372:11 376:13 377:9 382:10 383:8,20,22 384:1,3,4, 5,6,8,10,12,14,16,18,20 385: 1,1,2,2,19 NOAEL ^[4] 213:5 247:18 248: 22 249:16 nobody ^[3] 18:22 31:20 242: 18 nociception ^[1] 225:21 nominal ^[3] 264:18 278:7 286:1 non ^[1] 285:2 non-attempt ^[1] 16:20 non-CB ^[1] 199:4 non-CB1 ^[4] 59:11,12,17 188: 22 non-CB2 ^[1] 189:1 non-depressed ^[1] 289:3 non-descriptor ^[1] 301:20 non-diabetic ^[2] 81:7 82:10 non-directed ^[1] 98:9 Non-HDL ^[1] 83:20 non-obese ^[2] 227:21 228:16 non-pharmaceutical ^[1] 243:15 non-pharmacologic ^[1] 161: 12</p>	<p>non-placebo-controlled ^[1] 130:21 non-prescription ^[1] 161:13 non-responders ^[1] 279:5 non-rodents ^[1] 217:11 non-specific ^[1] 268:11 non-suicidal ^[1] 21:21 non-treated ^[1] 66:11 non-U.S ^[1] 278:18 Non-Voting ^[5] 2:19,21 8:7 9: 3 369:9 Non-zero ^[1] 24:7 nonclinical ^[9] 185:20 186:7 204:6,10 205:3 212:19 215:3 219:1 230:15 none ^[6] 66:13 126:13,19 286: 18 331:15 383:9 Nonetheless ^[5] 57:19 209: 13 265:15 285:19 368:21 nor ^[1] 110:4 norepinephrine ^[2] 183:11 194:19 normal ^[5] 70:7 128:18 160:4, 7 206:14 North ^[6] 39:2 255:12,16 259: 18 284:7 286:20 not ^[297] 9:6,20 18:15,17 19: 11,12 22:20 23:6,10,22 25:15 27:5,7,8,9 28:12,15 29:19 32: 15 34:7 38:6 40:13 41:2 43:5, 7 44:18 46:19 47:2,11,13,20 50:22 53:12 54:16 55:7 56: 11 58:13 60:7,11 71:14 73: 13 76:12 78:16 79:15 81:4 85:17 86:17 88:2 89:6,7,8 90: 5 91:20 96:20 97:10 98:10 104:7,9 105:9 108:2,3 111: 22 113:3,11 115:9,12 116:2, 15,21 119:1 122:3,6,14 123:1, 15 125:2,3,14 127:9,14,21 128:13,15,19 129:2,9,19,21 135:5 137:5,19 139:18,20 141:5,8 142:3 145:18 147:2, 12,13,16 148:22 149:12 151: 7 152:22 153:12 155:13 157: 5,8 160:18 161:5 165:14 169: 12 173:2,4,17 174:19 184:8 188:7,18 200:15 207:8 210: 10,13,14 212:9 214:19 215:1 216:6 218:7,7,22 219:7 221: 2 223:12,13,15 224:7 226:15 227:14 228:1 229:17 233:14 234:4 235:4,5,12 236:11,11 237:5,18,20 238:9,18 239:3,6, 6,15,16,21 240:2,4,14 241:1, 9,16 242:3,5 247:14 248:22 250:6,18 254:5,11 255:1,8 257:10 260:18 261:11,17 263:18 266:12 274:6 280:1,7 281:17 282:16 285:1,4 286:5 288:8 289:17 291:2,13 292: 15 293:18 294:6 295:20 296: 2,18 298:18 300:19,19 302: 22 303:10 305:2,6,7 306:18, 19 308:4,9 309:1,19 310:21 311:8 312:9 316:21 318:12, 17 319:1,7,14,19 320:19 321: 1</p>	<p>1 322:15 324:5,19 325:7 326: 14,14,20 328:6,18,20 332:14 333:5,16,21 335:4 336:15 337:20,21 338:10 340:2,20 341:12 342:10,17,19,20 344: 20 346:4,5 347:18 348:1,3 349:10 350:2,10,11 351:1,8, 14 352:19 353:5,5 359:5,6 362:7,14,20 363:1,6,7,9,16 364:7 366:6 368:6,10 369:12 371:6,10 376:4,22 377:9 378: 20 379:6,13,20 380:13,22 381:19 382:9,22 notable ^[1] 299:1 notably ^[1] 259:18 note ^[13] 9:1,10 18:16 23:21 47:11 66:13 95:15 102:7 120: 6 206:12 209:22 254:10 330: 13 noted ^[13] 10:2 120:17 126:4 145:6 148:12 208:12 215:2 218:17 233:12 255:19 264: 20 270:12 368:6 notes ^[2] 102:22 119:12 noteworthy ^[1] 60:13 nothing ^[7] 23:8 25:9 160:17 236:9 238:10 242:13 302:1 noticed ^[1] 310:8 notion ^[1] 332:15 notions ^[1] 16:22 notoriously ^[1] 80:22 Novartis ^[1] 9:18 novel ^[1] 334:9 November ^[1] 145:8 Now ^[86] 17:11 20:6 21:6 28:6 38:21 42:1 47:11 49:2 58:10 61:5,7 69:1 74:14 77:4 80:19 82:20 85:13 89:1,21 90:2,8 92:3 93:2 97:6 105:12 107: 18 108:10 109:15 114:1 128: 17 129:5 131:16 132:2 134: 14 136:7,20 137:1 138:3 140: 3 141:19 145:12,21 148:21 152:10 156:4 157:19 161:12 162:10 163:22 164:12 167: 19 183:13 185:3 191:22 215: 16 225:9 230:21 233:5 234: 11 237:15 240:19 246:18 256:2 284:1 293:11 294:8 295:11 300:1 306:8 315:3 318:20 326:5 330:10 333:19 334:6,13 338:9 345:22 353:5 359:21 371:5 374:2 375:6 377:2 379:14 382:22 nowhere ^[1] 17:21 nuances ^[1] 35:11 nuclei ^[1] 225:5 number ^[78] 31:22 38:9 40:4 41:5,19 45:8 48:7 53:5 63:5 95:13 126:20 131:15 133:4 141:4 156:6 161:9 169:12 171:2 174:20 179:13,14 187: 8,19 200:1 228:16 231:10 235:2 256:19 267:12 275:12 279:11 284:20 289:13,18 295:2,9,11,17 297:1 303:10, 14 304:19 307:9 309:20 310: 17,20,22 312:6 315:13 318:3, 14 327:14 328:3 332:20,20 336:16,17 339:20 342:4,5 343:13,14,17,18 344:5,7,11, 15,15 345:10,10,19 346:7,11 347:3,7,8 362:10 numbers ^[25] 21:10 33:14 41: 15 104:18,19 106:5 111:4 132:13,17 133:20 209:20 258:17 263:11 265:17 272: 12 281:12 294:20 310:17 327:18 328:14 338:21 363: 16 366:12,19 367:4 numbness ^[1] 268:14 numerous ^[1] 15:18 nurse ^[4] 34:21,22 119:7 371: 8 nutrient ^[1] 68:1</p>
---	---	---

O

O ^[7] 2:6 3:1 4:1 5:1 222:1,1,1
o'clock ^[2] 185:8,8
obese ^[51] 11:6 42:21 43:18
61:17 63:14 65:19,19,21 66:
9,11,17 69:21,22 70:10,12,16,
20 72:13,22 76:7,9,11 79:8,
10 83:1 91:20 98:4 114:13
134:10 135:4 138:20 159:4
160:14 166:3 168:9 227:18
228:2,14 234:3 244:16 245:
11,19 253:3 256:1,8 274:11
299:8 332:12 352:22 362:19
363:6
obese-treated ^[1] 66:12
obesities ^[1] 70:18
Obesity ^[121] 4:12 37:5 38:5,
19 39:1 40:7 41:4 46:17 47:8
50:3,7 51:14 52:14 61:7,14,
19,22 62:5,10 63:1 65:15 66:
21 68:7,14,17 69:13,18 70:2,
5,11 72:3 73:4,12,18 74:3,17
76:1 78:5 81:19,21 91:19 92:
14,20 93:18 94:13 95:8,14,16
98:15 99:14 100:6,12 102:4
110:10 112:12,16 113:1,7
120:11 121:16 124:7 138:12
146:18,21 147:1 151:15 157:
17 158:5,6,9,17,20 159:17,20
160:6,12,20,21 161:4 164:6,8,
13 166:19 168:1,12 180:20
183:13 190:4 199:13 214:12,
17 229:11 241:12,18 243:8,
11,12,17,22 244:3,6,8,12 245:
2,14,18 253:4 271:19 272:2,3
286:3 316:22 330:4 331:12
338:19 345:2 346:12 353:6
355:10 356:7 364:22
obesity-related ^[1] 160:11
obesity-specific ^[1] 91:5
objected ^[1] 316:11
objective ^[6] 84:7 305:22
307:6 322:11,14 342:7
observable ^[1] 217:2
observation ^[7] 172:19 173:
16 178:18 254:18,21 326:12
359:8
observations ^[3] 179:14 206:
16 369:14

observe ^[1] 145:14	42:4,6,12,12,12,15,16,21 43:	14,15,20,20,22 159:10,17	4,12,13,18,20,22 266:2,2,3,
observed ^[31] 67:15 70:3 80:	1,2,10,18,19 44:6,11,19,21,	160:1,4,12,16,20 161:7,9,11,	12 267:4,6,8,12,12,14,17,18,
9 83:6 84:1 104:21 133:21	22 45:7,9,10,11,22 46:3,5,6,	14,17,19 162:1,1,2,5,7,9,18,	19 268:1,2,6,7,7,8,11,18,18,
205:12 206:2,4,8,15,22 207:2,	11,17,22 47:1,6,14,15 48:7,	19,20 163:1,3,4,11,16 164:1,	18,19,20,21 269:3,5,7,8,15,
9 208:3 211:5,21,22 212:3	10,12,13,13,14,17,17 49:4,7,	1,2,5,7,8,13,15,22 165:1,5,7,	17,22 270:1,2,3,13,15,16,18,
213:1 216:19 218:10 247:11	8,11,14,16,16,16 50:1,2,3,6,6,	7,11,11,17,17,19,22 166:2,7,	22,22 271:3,4,6,7,8,9,11,16,
248:13,21 293:19 299:14	9,10,11,12,14,15,16,22 51:9,	14,15,18,19 167:5,9,14,16,20,	18,22,22 272:1,5,6,10,17,18,
322:14,19 340:21	11,12 52:1,3,6,7,9,10,12,18	22,22 168:8,11,14,15,17,20	21 273:7,17,17,19,21 274:5,8,
observer ^[1] 375:9	53:5,7,10,15,19 54:3,7,10,13,	169:7,9,12,18,19,20 170:4,10,	14,16,17,18,19,22 275:5,6,11,
obtain ^[6] 13:10 96:1 260:20	17,20 55:2,13,13,14,18 56:10,	18,20,22 171:2,9,14,16,22	13,13,16 276:3 277:5,15,16
282:21 309:3 373:10	11,13,15,21 57:2,3,11,15,22	172:6,8,9,18 173:2,4,6,8,11,	278:3,5,5,7,11,13,15 279:1,2,
obtained ^[9] 12:21 45:8 98:	58:3,5,7,8,14,19,22 59:7,8,10,	11,12,21 174:14,14,16,18,20	6,11,12,15,17,18,18,20,22
11 128:3 136:4 254:12 294:3	12,16,19,20,22 60:2,4,14,15,	175:17,22 176:5,5,12,15,18,	280:2,3,5,7,10,15,17,19 281:
375:8 379:16	17,18,20,21 61:1,6,8,16,19,	22,22 177:2,11,13,13,14,21	1,3,5,7,8,10,11,12,15,21,22
obvious ^[1] 20:16	21 62:6,9,21,22 63:5,6,15,16,	178:4,6,7,19,20,22 179:13,14,	282:13,14,19,21 283:5,11,14,
obviously ^[18] 11:12 21:10	17,20,22 64:3,4,7,11,22 65:3,	17,18,22 180:14,19 181:3,10,	17,18 284:1,3,4,6,20 285:2,9,
24:13 142:6 147:18 148:9	5,7,8,21,22 66:4,10,12,13,13,	19 182:6,10,11,12,14 183:2,	11,20,22 286:1,11,15,16 287:
150:3,15 151:22 154:14 172:	21 67:3,4,4,4,12,14,16 68:4,6,	10 184:5,6,20 185:6,14,16,18	8,12,16 288:7,16,17,21 289:2,
22 229:22 309:17 316:21	13,16 69:2,5,7,9,13,15,18,20,	186:3,3,5,6,7,10,10,16,19,20	2,4,11,13,18 290:1,3,5,7,15,
352:4 364:3 368:15 373:14	21 70:2,7,10,12,12,22 71:9,	187:1,2,4,6,8,10,14,15,19,19,	17,20,21 291:18,19 292:4,8,
occasional ^[2] 105:7 302:2	10,10,14,15 72:3,3,6,9,10,13,	21,21 188:2,3,14,17,18 189:9,	13,15 293:1,2,4,6,7,11,22
occult ^[1] 130:6	13,17,21 73:3,4,8,9,11,17,18	10,14,18,20,22 190:2,4,4,11,	294:6,21 295:2,9,11,13,16,17,
occupancy ^[1] 207:20	74:11,12,14,17 75:3,14,17 76:	14,19 191:6,19,21,22 192:2,3,	18,22 296:6,12,15,17,20 297:
occur ^[19] 113:11 122:6 170:	14,22 77:4,7,9,17 78:5,6,10,	10,12 193:9,11,13,22 194:4,	3,10,12,15,16,17,21 298:2,10,
2 175:19 193:15 195:16 198:	13,16,18,20,22 79:1,3,5,7,14,	13,14,15 195:1,6,8,18,20,21,	12,13,15,19,21 299:6,13,14,
8,14 200:8,14 206:10 212:14	20 80:2,9,11,12,20 81:12,13,	21 196:5,12,13,14 197:17,19	18 300:6,7,9,11,12,17,18 301:
213:7,15,22 254:6 278:1 343:	13,17,18,18,20,22,22 82:1,12,	198:13,18,19 199:8,10,16	1,7,8,10,13,14,15,15,16,17,
5 382:16	14,20 83:2,5,6,9,9,10,14,15	200:1,13,21,22 201:2,5,7,8,9,	20 302:2,3,3,19 303:6,6,11,
occurred ^[30] 17:5 99:18 115:	84:6,6,7,11,14 85:14,17,22	10,13,17,20,21,22 202:3,4,7,	11,12,13,15,16,20 304:19,20,
4,11 124:14 179:21 182:15	86:2,7,12,20 87:4,15 88:3,4,	12,15,22 203:3,6,6,10,10,11,	22 305:2,3 306:2,3,8,10,13,
205:21 211:15 253:21 258:3,	5,20 89:1,5,6,15 90:9,20,20	20 204:7,9,12,15,19,20,21	15,18,20,22,22 307:16 308:7,
4 262:9,14 263:8,14 264:3	91:1,2,7,10,10,14,14,18 92:7,	205:1,3,4,11 206:6,16,17 207:	20,21 309:2,3,4,6,12,13,22
271:5,11,16,19 272:19 273:6	14,15,15,19,20,20 93:7,9 94:	6,7,12,12,18 208:14,16,18,20	310:2,7,9,12,18,19 311:7,15,
283:16 285:7 286:17 313:15	2,3,10,14,15,21 95:5,13,16	209:14,17,20 210:4,6,10,22	20,21 312:9,15,17,19,21 313:
318:16 331:6 341:18	96:2,8 97:14,16 98:9,16,21	211:8,9,13,17,22 212:11,18	8,9,17,18,19 314:2,5,10,11,
occurrence ^[4] 27:19 110:17	99:12,15,17 100:2,7,8,21,22	213:2,15,15,16,18 214:8,12,	13,13,20 315:2,6,8,10,13,20
137:20 272:21	101:3,5,13,15 102:6,11,12,20	15,17 215:5,10 216:2,7,17	316:2,11,12,16,19 317:2,3,6,
occurring ^[10] 62:20 98:15,	103:2,5,14,18,20 104:2,3,7,	217:11,17 218:5,17 219:6,7,	7,12,13 318:2,3,9,11,12,14,
20 126:11 261:12 267:17	15,21,22 105:4,14,15,19 106:	17,18,21,22 220:8,12 222:2,8,	16,16,17 319:1,10,16 320:5,9,
272:1 277:10 283:20 286:16	4,4,5,8 107:2,13,19,20 108:1,	10,19,21 223:2,4,8,11,14,15	10,11,20,22 321:1,2,5,16 322:
occurs ^[5] 137:22 205:16 206:	3,4,7,8,15,18 109:4,12,21	224:2,5,7,9,11,12,17,19,21	5,9 323:5,10 325:9,10,15 326:
20 208:2 213:11	110:6,6,17 111:7,8,9,11,16	225:6,8,9,11,14,19,20,21,21,	4,12,14,17,18 327:1,4,10,12,
October ^[3] 45:13 46:11,15	112:4,17,18 113:6,7,13,13,18	22,22 226:2,5,7,11,20 227:4,	14,14,18,20 328:3,8,9,10 329:
odds ^[16] 114:6 116:15 259:	114:7,9,9,11,18,22 115:2,13,	4,5,6,19 228:2,7,9,9,9,11,12,	3 330:5,10,14,17,19,22 331:4,
17 285:20 286:11 288:21	17,20 116:5,8,13 117:9,9,11,	13,15,17,18,18 229:2,4,5,7,	4,9,11,14,15,18,21 332:1,12,
290:3 315:19 317:2,5 324:10,	16 118:10,17,18 119:4,9,16,	18,20,21 230:1,2,3,4,6,7,15,	16,20,22 333:1,3,8,9,14,14,
18 325:3,5,6,9	17,18,21,22 120:8 121:2,3,9	22 231:1,2,10,16,16,18,19,19	17 334:4,6,10,12,15,16,21,22,
OF ^[1900] 1:1 3:5,14,16,19,23,	122:11,15,21 123:3,7,9,10,22	232:6,7,8,13,17,19 233:1,3,	22,22 335:3 336:6,13,16,16
27 4:14 5:6,10,13,14,15,18 6:	124:4,5,11,13,16 125:2,5,6,	10,12,13,16,17,19 234:2,7,8,	337:1,14 338:21,21 339:20
6,7,9,15,17,22 7:1,8,9,13,13,	13,20 126:1,9,10,10,15,20	15,18,18,18,19,20 235:2,17,	340:8,12,22,22 341:7,9,9,11,
14,16,17 8:4,12,14,16,16,17,	127:8,10,12,18 128:8,12,19	17,18 236:1,6,15,20,22 237:3,	12,15 342:5,5,17 343:2,4,7,
18,21 9:4,14,17,17,22 10:4	129:3,5,9,11,13 130:1,8,15,	7,10 238:3,5,8,10,12,13,16,	11,15 344:2,13 345:17 346:3,
11:8,9,14,15,20 12:1,7,7,9,11,	16 131:15,21 132:8,12 133:5,	17,21 239:1,7,11 240:5,6,8	4,14 347:5,5,5,7,15,19,21,22
12 13:4,5,12,13,20,21 14:2,4,	8,11 134:12,15,20 135:6,7,8,	241:10,11,15,22 242:8,9,16,	348:6,9,14,18 349:6,13,13,19
6,21 16:10,11,16 17:4,5,12,	11 136:3,6,17 137:2,2,9,16,	20 243:16,17,17,18,22 244:3,	350:12,16,16,20,22 351:4,9
14,18 18:1,5,19 19:5,8,17,19,	20,21 138:3,4,4,5,6,7,11,14,	7,9,13,15,17,18,19,20 245:3,	352:10,15,20 353:12,14,16,
21 20:7,9,12,18 21:3,6,15 23:	17 139:1,5,6,8,16,16 140:10,	7,11 246:3,16,19,20 247:4,19	20 354:15,15,17,18,21,22
6,6,12,20 24:9,16 25:6,15	11,16,18,22 141:4,8,21 142:4,	248:20 249:13,14 250:3,11,	355:13,18,22 356:11,14,15,
26:8,10,14,17,19 27:2,11 28:	5,12,14 143:13,19,22 144:3,9,	18,22 251:8,10,19 252:5,7,9,	21 357:1,1,3,5,6,9,10,21 358:
3,9,11,18 29:3,6,12,13 30:22	10,18,19,21 145:4,4,6,8,9,22	12,13,13 253:2,5,8,13,13,16,	2,2,6,9,20,22 359:1,4,20,22
31:2,6,8,9,18,22 32:2,4,10	146:10,21 147:11,13,15,18,	22 254:2,4,12 255:6,13,20,22	360:2,14,21,21 361:1,2,13,15,
33:2,4,5,6,11,12,22 34:13,21	20,21,22 148:2,7,9,13,16,19	256:5,6,17,19 257:2,5,8,8,9,	16,17 362:1,5,9,10,12,13,18,
35:1,3,4,8,11,16,20 36:5,11,	150:7,8,9,18,21,22 151:11,14,	14,15,22 258:1,8,9,12,16,21	19,20,22 363:4,5,9,10,11,12,
19 37:3,4,4,14,14,15,18,18,	22 152:8,14,21 153:3,5,6,7,	259:1,4,5,10,15 260:13 261:4,	13,14,19 364:19,19 365:9,14
20,21 38:4,5,7,8,9,18,18 39:3,	13,17 154:9,12,14 155:3,11	10,12,13,15,16,18,20 262:1,3,	366:2,12,18,18,20,20,22 367:
4,7,12,18,21 40:4,11,17,21,	156:3,11,12,17,21 157:8,15,	8,13,14,20,21 263:6,10,15,20	1,1,2,3,12,13,20,21,22 368:5,
21 41:3,4,5,7,11,12,14,17,20	17,21,22 158:4,5,6,8,11,12,	264:2,7,13,13,14,18,22 265:1,	12,19 369:1,5,15,18,21,22

<p>370:1,2,14,21 371:21 372:6,8,11 373:13,16,17,21 374:19</p> <p>375:1,4,14,19 376:7,8 377:1,2,5 378:4,6,19,21 379:2,2,3,5,12,19,21 380:20 381:6,9,14,20,21 382:6,9,13,17,18,21 383:8,10,17 384:22 385:10,11</p> <p>off ^[12] 160:7,8 198:10 241:16,20 242:1 338:2 347:13 353:15,16 371:9 374:19</p> <p>offer ^[1] 170:3</p> <p>Office ^[3] 6:7 236:5 237:14</p> <p>Officer ^[1] 12:2</p> <p>officially ^[2] 351:18 385:20</p> <p>offset ^[1] 357:20</p> <p>often ^[25] 16:21 24:7 29:15 33:19 105:4,5 107:5,8 122:9 125:9 126:5 135:13 149:11 160:22 243:1 256:14 268:10,11 280:15 300:17 302:18 321:4,8 348:5 353:7</p> <p>Oh ^[3] 236:10 250:13 323:1</p> <p>Ohio ^[1] 380:21</p> <p>Okay ^[11] 10:9 13:19 21:17 36:9 221:4 250:2 338:3 340:4 372:18 374:3 384:21</p> <p>older ^[4] 255:14 278:14 328:6 365:8</p> <p>olfactory ^[1] 225:2</p> <p>ominous ^[1] 233:1</p> <p>on ^[454] 4:8 5:22 6:1 8:19 9:3,5,20 10:17 11:2,19 12:16 13:1,12,21 14:20 15:11 16:22 26:5,16 27:16 29:10 33:1 34:20 37:10 38:18 39:3,8 42:5,19 44:12 45:17 46:5 47:21 48:4 51:3,22 52:9,22 53:12,19 54:2,21 58:22 60:5 61:15 64:3,8,13 65:5 67:8,10 69:4 70:12 71:7,15 72:13 73:4 75:2,3,6,15,18 77:9,10 78:6,19 79:21,21 81:3,16 83:4,6,8,22 84:16,18,21 85:1,3 87:1,4,6 88:2,18 90:3,11,13,14,17,22 91:8,11 93:17 94:3 95:2,8 96:3,11,13,14,15 97:22 98:11 100:21 102:7,10,18 103:6,21 104:12,19 106:3,10,16,18,20,21 109:1,16 110:8 112:4,13 113:19,19 116:20 118:8,9,14,22 119:18,22 120:13,17 122:5,7,19 123:2,10 124:13 126:2,9 128:16 130:14,17 131:2 132:12 133:8,14,15 135:5,6,10 136:4 137:1 139:11 140:8 141:21 142:14 144:15,17 147:10,16 148:7,9,22 149:18 151:10 153:18 154:16 155:17 156:6 157:2 163:11 165:5,20 169:6,13 170:19 171:14 172:14 174:3,18 175:11,14 176:14,14,15 177:6,13,15,22 178:3,11 179:3,4,6,7,14,21,21 180:11,14 181:9,21 184:20 185:21 186:5,8 187:13,22 188:6 192:14,16 194:6,9,17,</p>	<p>19 195:15,22 198:10,16 200:13 201:14 207:7 208:6,8 210:4,10 211:2,13 213:13 215:6 216:9,22 217:7 218:13 219:4 222:5 224:10,13,17 225:9,9,11 226:2,3,16 228:5 229:6 230:1,9,13,22 231:9 232:12,15,18,22 233:20 234:21 235:10,16,17 236:4,8,8 237:9 238:6,19 239:18 240:2 241:2,15 242:11,22 246:4,10,21 247:6 248:7 249:6 250:7,16,20 251:4,18 252:15,15 254:12,18 256:14 257:15,19 258:1 259:6 261:5 262:15 265:4,20 266:8 267:22 269:7 271:1,1,2,16,17,17 272:11,12 275:4,20,20 276:6,12 277:3,6 279:15 280:18 281:6,9,12,14 282:13 283:16,20,21,21 284:21 285:2,5 286:17,18,22 287:1,10,11,22 289:3,6 294:10,14 296:14,16,18 297:2 298:14,17,22 303:21 304:5,8,10 305:16 306:4,13 307:15,19 309:18,22 310:21 311:20 313:14 314:4 315:7,8 316:5 317:11,18 318:6,7,10,13,20,21 319:3,3,10 320:9 323:12 327:4,16 329:7 331:2 333:12,19 335:3 336:3,6,22 338:19 339:8,11 340:13,20 345:5 347:2 348:14 350:5,6,15 352:3,9 353:2,2,20 357:4,15,20 358:17 359:14,21,21 360:5,8,19 361:12 362:7,17 365:10,12 368:14,18,20 369:14,21 370:2 371:15 373:8,15,15 374:13 375:13 376:18 378:13,15,16,19 379:1,7,14 380:4,6,13,13,22,22 382:10 383:11,13,14 385:1,2,6</p> <p>on-demand ^[1] 269:15</p> <p>on-scoring ^[1] 136:21</p> <p>once ^[8] 42:8 143:15 147:19 173:12 224:12 239:14 252:21 304:1</p> <p>once-a-day ^[1] 42:20</p> <p>one ^[158] 9:7 13:6 17:17,18 18:5 20:12 28:1 29:13,22 31:1,2 36:5 39:18 47:5,21 55:13 56:2,7 63:18 71:5 74:21 79:6,21 80:3,12 84:17 85:3 100:3,3 115:14 116:20 117:11,20 118:15 120:15 121:19 123:17 126:12,16,22 127:8,11,12 128:12 132:14 135:2 136:10 139:6 142:10 144:13 145:4,18 147:21 148:13 149:15 150:7,12 151:8 152:8 154:3 156:4,5 162:9,14 163:2 169:7 170:17 172:5 174:2 175:10 176:12,21 178:12 180:8 181:11 204:16 216:11 222:13 223:18 224:5,11,17 233:21 234:12 238:12,13 244:13 247:6 248:18 252:7 253:20 254:22 256:22 258:16 260:</p>	<p>13 265:22 267:19 268:2,4,5,22 271:2 277:13 282:12 286:15 293:3 294:5 296:6,19,19 303:15 306:8,22 311:1,2,6 314:2 316:18 320:20 321:7,13 322:8 323:1 324:21 325:21 329:12 331:8,16,22 332:6,20 335:6 338:18,20 341:2 342:11 344:9 352:4,19 355:8 356:8,20 357:15 362:19 366:14 367:6 369:11 370:2,13 373:1,13 374:19 376:13 379:2,12 380:2 383:19 384:22</p> <p>one's ^[1] 24:17</p> <p>one-minute ^[1] 327:9</p> <p>one-third ^[1] 26:8</p> <p>one-way ^[1] 192:13</p> <p>one-year ^[3] 77:2 253:2 336:21</p> <p>ones ^[9] 136:14 153:14 180:6 217:7 321:20 345:16 346:1,1 360:4</p> <p>ongoing ^[30] 29:16 40:18 41:8,21 45:15 94:5 97:14,21 100:16 117:10 118:6 119:14,16 120:2,16,19 121:1,13,22 133:10 136:9 148:7 168:18 272:9,22 273:8 275:22 286:22 299:4 310:18</p> <p>only ^[58] 15:17,19 19:10 24:9 27:21 31:3 32:15 38:6 56:14 57:10,16 58:18 63:22 66:10 71:17 96:18 97:3 115:18 116:11 129:21 130:15 138:6,17 141:5,8 142:3 147:3 149:12 157:8 161:5 163:1 181:16 189:7 207:8 242:6 244:5 255:1 257:19 258:18 260:8 274:6 275:19 284:10 296:5 304:9 306:4 309:9,12 318:11 334:12 343:10 346:11 347:12 351:7 363:10 368:6 375:7 382:9</p> <p>onset ^[1] 167:5</p> <p>onto ^[3] 34:10 192:8 328:20</p> <p>Open ^[14] 4:2 8:11 11:22 94:22 98:7,8 102:1 185:9 215:16 221:5 222:14,19 223:2 372:21</p> <p>opens ^[1] 192:20</p> <p>operation ^[1] 162:21</p> <p>operational ^[1] 30:17</p> <p>operative ^[1] 290:2</p> <p>ophthalmologist ^[1] 266:22</p> <p>opinion ^[4] 160:18 164:19 331:16 369:10</p> <p>opioid ^[1] 195:12</p> <p>opportunities ^[2] 236:18 385:15</p> <p>opportunity ^[3] 46:8 151:20 246:13</p> <p>oppose ^[1] 267:8</p> <p>opposed ^[1] 27:20</p> <p>opposite ^[3] 35:3 60:15 197:6</p> <p>optic ^[2] 127:12 268:2</p> <p>optimal ^[1] 34:7</p>	<p>option ^[4] 160:19 169:19 356:8,11</p> <p>options ^[5] 73:2 160:17 161:16 170:5 245:1</p> <p>Oquendo ^[1] 16:2</p> <p>or ^[311] 9:20 10:5 13:5,18 15:21 16:16,19 20:7,10 21:10 22:3,16 24:1,12,16 28:20 29:22 30:9,19 31:5 34:3,10,14,21,22 35:1,14 36:7 38:15 39:13,13,14 40:5 42:1 43:13,19 45:19 46:18 47:15,16 48:4,4 53:2 55:20 57:15 63:8,15,22 64:5 69:22 70:17,19,21,21 72:22 73:21 76:9,11 77:11 78:12,13,13 81:4 82:1,1 84:2,3,18 85:18 87:7,10 89:8,22 91:17,17,19,19,20,21 95:11 96:7 97:17 99:19 102:6,14,14 103:3 104:1,5,9 107:12 108:3,5,17 109:22 110:2,10,11,21 112:2 113:9 114:22 115:12 116:4 118:4 119:5,19 123:15 125:4,5,6,10,11 129:9,19 130:21 131:7,8,13 132:3 133:15,19 135:19 136:14 138:6 141:1,5 143:3 144:20 145:1 147:16,17 149:22 150:1,5 152:5 153:12,13 154:18 160:14,21 163:7 166:9 169:15 170:10 173:5 178:14 179:21 181:22 182:9 183:17 186:4,14 187:20 188:8,9 195:10 196:13 198:9,10 199:3,12 201:16,17 205:16 206:19,21 207:3 208:1,7,7,11 211:6 212:22 216:2 218:1,21 219:12,22 220:12,21 222:13 223:3,9 224:20 225:17 227:1,2,13 228:1 229:8 231:14 236:22 238:9,12,13,17 239:4,19 241:11,11 242:9 247:14 249:8 250:10 252:12 253:13 257:18 258:7 265:20 266:15,22 267:4,6,7 268:21 269:16 270:4,15 274:9,17,18,18,19 275:6 276:7,9 280:20 281:1,2,7 283:8,14 286:5 288:2 291:2 292:6 294:14 298:22 299:11 300:15 301:2,7 302:3,5 305:13 306:3,4 307:9 308:4 309:19 310:5 311:11 312:1 313:21 314:14 316:3 320:1,16 321:4,13 324:5 325:15 326:7,20 329:8 330:15,18,20 332:9 333:1,4 334:17,17 335:4,4,7 339:2,17,18 341:13,13,13 342:19 344:20,21 346:9,17 348:1,2 349:12 350:3 351:3 352:16 353:4 355:15 357:1,4 363:6 368:10 371:7,8,8 374:5,8,18,21 375:9 376:1 379:13 382:17</p> <p>oral ^[4] 87:9 88:9 223:3 381:21</p> <p>orange ^[1] 56:9</p> <p>Order ^[14] 3:2 5:2 23:6 115:6</p>
--	--	---	--

<p>121:2 123:10 124:13 129:18 167:13 222:2 259:20 309:3 316:6 334:6 ore ^[1] 180:8 orexigenic ^[3] 199:11 202:13 214:16 organ ^[3] 205:3 230:17 302: 14 orient ^[1] 11:10 origin ^[1] 100:8 original ^[13] 15:15 108:7 110: 22 174:15 175:8 183:13 218: 17 260:14 270:21 282:12 310:16 325:9 339:14 originally ^[4] 21:16 183:7 189:7 197:12 orlistat ^[13] 73:21 161:22 182: 21 229:8 255:9 294:18 295:5, 6,15 296:2,13 328:12 330:15 ostensible ^[1] 130:6 osteoarthritis ^[2] 70:19 72: 12 osteoporotic ^[1] 166:8 OTC ^[1] 73:22 other ^[140] 9:20 10:3 22:9 27: 12 29:17,22 30:1,5 31:5,6,16 33:22 34:3,13 36:7 52:18 53: 3,6 73:19 79:1 81:4 95:10 102:14 105:12,22 107:18 109:20 115:10,14 116:1 122: 8 139:7 147:18 149:6 150:12 153:6 154:13,16 157:13 159: 20 160:10 161:8 165:2 166: 21,22 173:5 175:5 187:8 188: 22 191:7,8 192:5 195:6,9,9 199:4 201:4 211:19,22 213: 21 214:18 216:1,16 217:19 219:15 220:21 222:10 223:9 224:12,20 226:11,14 228:21 230:5,11 231:2,10 233:19 234:1 236:22 237:4 238:12 239:4 240:3 242:2 244:11 245:22 246:11 250:10,21 253:4 254:7 263:10 282:16, 19 288:13,20 289:11,12 294: 13 301:19 303:11 304:5 314: 16 317:9 320:1 321:14 322: 22 328:10,10 330:10 331:17, 19 333:20 337:9 340:10 341: 14 345:16 347:22 350:8,14 352:3 355:3 356:19 357:20, 21 359:14,22 363:3 368:7,11 370:5 373:9 376:16 377:11 378:2 380:14 382:16,17 383: 5 others ^[14] 20:7 23:7 146:6 212:5 232:8 281:16 288:5 332:16 351:16 356:16,17 367:9 369:21 370:16 Otherwise ^[2] 34:5 90:2 our ^[74] 5:8 13:14,21 14:7 25: 4 36:12 37:12 40:6,16,19 41: 21 44:6 45:16 46:15 69:14 74:16 85:14 93:21 96:16 116: 18 119:15 134:14 137:13 144:7 145:1,14 146:3 162:15 167:20 170:8,19 174:8 175:4</p>	<p>185:2 189:11 190:6 196:12 215:1 236:5 242:22 243:7 245:16,18,18,19 246:14 256: 14 258:17,22 270:9 271:6 277:12 281:15,20 284:2,6 286:6,6 292:19 297:2,3 298: 2,8,10 299:18 306:8 310:16 324:12 325:9 329:19 335:1 337:5 375:18 376:6 ours ^[1] 266:2 out ^[75] 25:5 41:11 80:16 81: 18 104:21,21 133:13 137:15 143:8 152:6 169:22 172:2,5, 6 173:10,12 174:21 183:1,9 184:8 203:8 228:9 233:8 234: 10 237:6,15,16 238:11,15 239:10 241:10 252:16 257:2 258:6 263:16 275:19 285:6, 19 286:8 288:7 290:14 292:3 293:7 297:4 301:21 311:20 312:16,21 314:5 315:22 319: 2 325:15 326:6 328:2 330:19 333:17 337:8 345:12 347:20 352:20 356:8,11 358:21 359: 11,15 360:21 370:16 374:5,6, 20 375:10 376:22 377:5 383: 10 385:11 outcome ^[8] 65:13 102:18 118:7 165:5 299:4,11 370:8 377:21 outcomes ^[10] 31:14,15 98:1 100:17 165:2 259:6 260:1,4 290:20 299:7 outlined ^[2] 37:7 82:14 outward ^[1] 119:5 over ^[45] 14:8,11 32:5 55:9 63: 16 66:13 69:20,21 70:3 75:4 76:2 78:2,2 83:6,7,10 86:19 88:3,8 94:9 98:17 104:17 109:5 116:6 117:6 122:21 135:22 158:3 163:11 165:19 176:20 182:1 225:2 229:20 232:18 240:7 266:2 274:21 295:13 296:6,14 308:7 359: 17 368:5 381:22 over-estimating ^[1] 347:9 over-the-counter ^[2] 337:11 352:4 overactivated ^[2] 62:7,10 overactivation ^[2] 68:6 164: 5 overactivity ^[1] 158:20 overall ^[32] 25:10 37:21 40:2 79:10 94:2 98:3 99:11 106:6 108:6 114:6,8 116:3,13,14 122:11 125:22 131:1 134:15 139:8 148:1 164:2 197:1 256: 18,19 261:10 262:9 264:2 277:1 324:20 344:14 358:7 366:14 overdose ^[4] 18:1,2 20:10 24: 20 overestimate ^[1] 270:8 overestimation ^[1] 26:19 overlook ^[1] 337:6 overriding ^[1] 277:22 overstimulated ^[1] 51:13</p>	<p>overt ^[1] 120:7 overview ^[5] 10:11 11:8 49: 16 185:20 186:7 overweight ^[23] 11:6 69:22 72:22 74:20 76:7,9,12 83:1 91:17,20 138:12,20 160:14 166:3 168:9 253:3 256:1 274: 11 352:22 353:6 362:19 363: 6,14 own ^[2] 118:14 361:3 Oxford ^[1] 234:10</p> <hr/> <p style="text-align: center;">P</p> <hr/> <p>P ^[4] 3:15 5:1 222:1 227:10 p-value ^[2] 317:3,6 p.m ^[4] 8:11 221:5,8 385:21 package ^[10] 44:2 82:7 137: 13 152:19 153:8 177:5 204:9 217:12 310:7,11 page ^[6] 170:19 171:14 177: 22 226:16 318:21,21 pages ^[1] 306:11 pain ^[6] 60:19 70:19 123:19 179:1 191:13 202:7 painful ^[1] 70:11 pair ^[1] 65:21 pair-fed ^[2] 326:3,13 palatable ^[1] 190:2 pan ^[1] 183:9 panel ^[8] 36:8 64:8 75:2 83:8 86:20 328:17 353:20 369:5 panic ^[5] 122:18 123:1,18 226:17 312:20 paper ^[2] 58:20 386:1 papillitis ^[1] 127:12 paracrine ^[1] 188:10 paracrine/autocrine ^[1] 193: 21 paragraph ^[1] 182:11 parallel ^[6] 70:2 76:16 81:17 88:5 90:4,12 parameter ^[1] 89:16 parameters ^[3] 68:13 348:15 359:22 paraphrase ^[1] 343:3 parasomnia ^[1] 276:18 paresthesia ^[2] 124:13 262: 18 paresthesias ^[4] 99:16 100: 10 124:16 136:12 Parkinson's ^[2] 125:2 304:7 parkinsonism ^[1] 304:21 Parks ^[7] 2:22 6:1,4,8,8 13:20 14:18 parosmia ^[1] 262:21 part ^[33] 8:17 12:3 33:12 34: 21 44:19 45:22 79:22 94:15 95:16 103:18 109:21 124:5 132:12 142:7,12 147:20 153: 7 167:20,22 175:22 185:14 201:2 206:16 217:11 228:17 237:7 246:22 306:15 327:1 328:3 337:14 363:21 366:18 partial ^[5] 196:17 206:4 319: 18 320:16 321:4 partially ^[4] 68:9 180:5 244:5 361:9 participant ^[1] 9:21</p>	<p>PARTICIPANTS ^[8] 2:1,21 9: 22 10:3 254:13,20 256:20 278:18 participate ^[1] 9:11 participated ^[2] 48:9 150:21 participates ^[1] 200:20 participating ^[3] 9:2 143:12 336:19 particular ^[18] 9:7 12:13,15 21:13 84:16 196:8 199:2 227: 17 244:13 258:3 327:19 329: 4,6 344:12 358:17 371:10 381:8 382:2 Particularly ^[10] 55:9 78:1 198:19 242:6 261:2 304:19 336:7,14 362:22 366:10 parties ^[1] 36:21 partly ^[1] 235:16 partner ^[1] 238:21 parts ^[2] 150:11 224:20 passive ^[2] 35:13 36:1 past ^[32] 31:19 47:14 48:4 103:19 104:2,14 105:4,15,22 106:3,11,14,17,19,22 107:4, 19 108:8,11 113:13 118:10 119:9 123:8 147:13 149:22 158:3,8 166:1 167:7 183:17 184:10 350:22 pathological ^[3] 52:13 266: 18 273:14 pathology ^[1] 230:18 pathophysiology ^[4] 158:20 164:8,13 168:11 pathway ^[1] 195:19 pathways ^[1] 164:1 Patient ^[114] 7:10 17:19 18:4 19:9 21:10 22:14 24:20,22 38:13 40:2 44:2 47:2,12,13, 20 70:11,13 72:4,14 89:4 91: 13 94:19 96:2,3 97:18 102:2 103:2 108:1 110:20 117:4,5, 12,21 118:13 119:6,7 121:20 123:18 126:13 127:19,22 128:12,16,17,20 131:15,17 134:20 139:13,14 141:6,17, 20,22 142:8,20 145:3 148:3, 15 149:12 150:8,12,17 151: 20 152:4,8,11,15 154:17 155: 1,18,22 157:4 159:2,10 161:4 166:8 168:1,4 171:20 172:4 176:14 180:20 181:18 228:8 246:5 256:7 258:20 266:1,6 272:4,5 281:15 282:10,14 283:11 301:13,20,22 307:10 311:2 323:3 328:1 348:2,6 353:7,12 361:12 366:22 367: 1 374:17 375:9,10 379:13 patient's ^[1] 142:18 patient/physician ^[1] 142: 11 patients ^[283] 26:10 38:9,14 39:12,16,20 40:5,6,7,9,17,18, 19,22 41:11,21 42:14,21 43: 18 46:18 47:4,15,16 48:1,3 62:19 70:16,20 71:3,6,9,14 72:22 73:9 74:5,20 75:10 76: 2,7,9,12,18 77:9,14,17 78:2,</p>
--	---	--	--

<p>16,19,20,22 79:10,12,16 81:1, 22 83:1,3 84:2,3,10,16,20,22 85:10,22 86:8,9,12,17 87:12, 15,17 88:2,11,18 91:3,8,11, 15 92:11 94:17 95:13 96:11, 19,22 97:12,15,22 98:16 100: 17 102:13 103:22 104:7,13 105:3,18 106:3,11 107:18 108:2,4,13 109:1,10 111:17 113:17,19 114:13,20,21 116: 6 117:6,17 124:15 125:4,13 126:1 129:6,8,11,16,20 134: 11 135:2,5,7 136:19 137:5,17 138:13,19,20,21,22 139:15, 18,19 140:11,12 143:11 144: 15,19 145:10 146:4 147:11, 13,15,22 148:7 149:8 151:10, 13 152:1 154:4 155:12 156:5, 7,8,12 157:6,14 159:3,4,12, 13 160:10,14,19,22 162:15, 17 163:1,4 165:11,19,20 166: 1,4 167:4,7 168:9,20 169:20, 22 170:5 172:6,20 173:4,7,10, 15 174:1,3 176:13,17,18,20 177:2,7,14 178:13,14 179:9, 13,16,17,18 180:1 181:2,21 182:1 183:15 184:1 226:20, 21,22 228:1,19 229:6,7,12 244:22 246:8 254:14,17 257: 5 265:21 267:3 268:13 272: 20 274:1,11 275:5 280:1 284: 9 288:6,11,14,18 289:1,3 290: 15 292:12 293:4,6 299:8 301: 13 306:16 309:9,13 311:19, 21 314:4 319:2 334:17,18 336:16,22 339:8,15,16,20 341:8 342:1 343:7 344:2 346: 4 352:22 353:7,13 356:11,22 357:16 358:2 366:20 367:1 370:1 374:6 377:2 378:14 379:18 380:3,13</p> <p>pattern ^[1] 174:20</p> <p>patterned ^[1] 151:1</p> <p>Paul ^[21] 2:18 3:20 6:17 37:19 93:2,13 179:10 220:10 249: 11,12 250:2 325:21 336:5,9 338:14 339:1 340:1 369:20 374:12 376:10 383:12</p> <p>pay ^[1] 240:15</p> <p>paying ^[1] 240:6</p> <p>payment ^[1] 223:8</p> <p>PCP ^[1] 197:18</p> <p>Pediatric ^[10] 8:2 14:3 17:13, 16 19:2 26:4 28:7,9 183:22 184:6</p> <p>pejorative ^[1] 16:21</p> <p>pending ^[2] 44:11 119:11</p> <p>Penn ^[1] 29:13</p> <p>pentylene tetrazol ^[1] 210: 20</p> <p>people ^[99] 5:22 8:10 13:18 24:6,7 26:8 27:16 30:12 33:9, 10,11 34:9 35:3 69:20 161: 15 169:12 171:16 174:16 180:11 183:17 185:2,10 212: 14 223:17,20 227:12 233:2 234:4 236:14,18,21 237:1,2,</p>	<p>18 239:11,15,18 240:3,6,12 241:10,14,15,20 242:11,17, 17,22 243:2 244:16 245:9,12, 19 251:2 281:5 293:12 306: 18 308:6 313:4 318:1,4 319: 16 320:21 330:2 332:8,20,22 333:7,10,18 339:16 340:12 349:22 350:2,21 351:2 352: 22 359:1,11 360:8 361:14 362:5,20 363:4,5,9,11,16,18, 20 364:1,3,20 372:10,22 373: 9 376:8 378:22 379:7</p> <p>people's ^[1] 340:16</p> <p>per ^[10] 75:10 78:16 109:10 117:5 131:15 156:7 259:10 272:3,4 293:4</p> <p>Per-study ^[1] 259:9</p> <p>perceive ^[1] 148:1</p> <p>perceiving ^[1] 301:20</p> <p>percent ^[185] 25:14 33:7 42: 19 54:17 63:17 64:1 66:10, 12 69:20,21 71:10,11,16,17 72:6,10,20,21 74:8 78:16,18 79:3,5 82:1,5,8 83:5,7,9,11, 17,18,21 87:1 88:3 98:16,17, 20,21,21 99:1,4 103:10,11,15 104:3,14,16,17 106:8,9,9 108: 9 113:7,13 116:1 119:22 121: 17 122:19,21,22 123:11,12, 14 124:12,14,19,22 125:5,6,8, 13,14 126:1,2 133:18,19 144: 19 145:9,9,12 162:16,18,19 163:1,2,4,7,8,9,10,13 169:9 171:1 174:13 176:5,7,12,15, 19 177:1,2,8,14 227:9,9 228: 15 229:7,19 244:20 252:12, 13 253:1 254:1,1,2 261:12,13, 18,20 262:11,11,14 263:10, 12,12,14 264:4,4 269:22 270: 1,3 275:7,18,18,20,20 277:5, 6,18,18,19,19,20,20,21 279:4, 8 280:5,17,18 281:3,5,8,10, 12 290:10,10 293:1,2 295:18, 19 296:5 300:9 313:18,19,22 318:9,11 330:17 332:1 333:1, 4,8 337:3 343:15,16 344:2,4, 11,11 345:20,20 366:20 379: 20</p> <p>percentage ^[4] 62:21 290:15, 17 293:6</p> <p>performed ^[23] 74:20 75:9 95:7 114:2 119:18 123:22 131:6 162:22 204:18 206:17 210:3 217:15 232:7 259:7 260:4 266:15,17,21 271:12 278:10 284:15 310:6,12</p> <p>performing ^[3] 163:16 219:8 269:6</p> <p>performs ^[1] 192:1</p> <p>Perhaps ^[8] 60:1 130:6 184:1 216:8 290:12,20 331:9 357: 13</p> <p>period ^[9] 50:14 76:22 80:16 112:11 114:22 115:2 128:22 232:18 337:1</p> <p>Periodic ^[1] 45:19</p> <p>periods ^[2] 233:3 367:3</p>	<p>peripheral ^[18] 52:4,10 61:13 64:5,7 65:4 67:8,10,15 186: 17 189:16 191:13 200:21 201:10 220:8,12 261:6,7</p> <p>peripherally ^[4] 101:3 220:1, 5 326:17</p> <p>periphery ^[6] 189:8,13 199: 12 201:7 219:20 225:6</p> <p>permanent ^[1] 176:2</p> <p>permitted ^[1] 20:15</p> <p>persists ^[1] 272:14</p> <p>person ^[4] 30:9 180:12 302:4 351:12</p> <p>person-year ^[2] 271:21 272: 1</p> <p>personal ^[1] 15:21</p> <p>personality ^[2] 17:18,21</p> <p>personally ^[3] 348:11,21 381: 11</p> <p>persons ^[2] 145:2 245:18</p> <p>perspective ^[11] 15:11 33:1 70:10 72:2 89:5 137:8 163: 14 172:14 182:7 251:13 349: 18</p> <p>pertain ^[1] 260:14</p> <p>pertinent ^[1] 308:12</p> <p>petit ^[5] 130:3 319:13,15,17, 18</p> <p>Peto ^[3] 114:5,5 116:12</p> <p>Pfizer ^[3] 8:6 9:8,8</p> <p>Ph.D ^[9] 2:7,8,9,17,24 3:10,13, 22,28</p> <p>pharmaceutical ^[5] 15:18 18:18 25:16 26:5 243:15</p> <p>pharmacists ^[1] 152:2</p> <p>pharmacodynamic ^[2] 74: 19 295:22</p> <p>pharmacokinetics ^[3] 42:12, 17 250:6</p> <p>pharmacologic ^[7] 187:6 196:14 199:8 203:11 212:8 214:4,14</p> <p>pharmacological ^[1] 49:22</p> <p>pharmacologically ^[1] 330: 3</p> <p>Pharmacologist ^[2] 6:15 11: 18</p> <p>pharmacology ^[11] 40:6 53: 22 54:10 112:6 186:5 194:4 203:16 204:3,11 218:18 225: 11</p> <p>pharmacotherapies ^[1] 245: 2</p> <p>Pharmacotherapy ^[2] 73:8 74:10</p> <p>pharmacovigilance ^[2] 143: 1 215:7</p> <p>Phase ^[44] 39:9 40:6,19,20 42:15 74:22 75:8,18,22 93: 17 94:1,1,10,11,12,16,21 95: 14 109:7 110:7,7,12 112:15, 15 115:1 119:14 129:6,6,14, 14,14,16 131:5 134:4 136:20 145:22 180:19 259:8 260:21 265:8 284:9 334:11 338:18 377:7</p> <p>phases ^[2] 130:21 225:22</p>	<p>phenomena ^[1] 171:18</p> <p>phenomenon ^[1] 171:3</p> <p>phentermine ^[2] 73:19 229:8</p> <p>Phil ^[2] 354:6,8</p> <p>Philadelphia ^[1] 6:19</p> <p>Philip ^[1] 7:12</p> <p>Phillip ^[1] 2:17</p> <p>phobias ^[1] 273:15</p> <p>phosphorylation ^[1] 195:19</p> <p>phrase ^[1] 226:9</p> <p>physical ^[8] 73:6,15 90:22 91: 7 178:3,15,21 358:6</p> <p>physician ^[17] 89:4 141:20 148:4,21 149:18 150:12 151: 21,22 152:4,8,10,14,19 155: 18 301:12 306:4 371:9</p> <p>physician's ^[2] 141:13 237: 14</p> <p>physician-patient ^[1] 141: 19</p> <p>physician/patient ^[1] 154:8</p> <p>physicians ^[23] 73:20 135:8 143:8,11 144:13 145:3 146:4 148:15 149:2,7,11 151:10 153:1 155:6,11,12 156:9 157: 6,14 181:5 246:7 334:15 352: 5</p> <p>physiologic ^[1] 225:13</p> <p>physiological ^[4] 51:11 67: 22 164:16 188:15</p> <p>physiology ^[1] 219:18</p> <p>pick ^[1] 347:20</p> <p>picked ^[1] 333:8</p> <p>picture ^[3] 122:1 230:2,4</p> <p>piece ^[1] 24:9</p> <p>Pierre ^[2] 3:18 69:1</p> <p>piggyback ^[1] 376:18</p> <p>piggybacked ^[1] 328:20</p> <p>pill ^[1] 235:22</p> <p>Pittsburgh ^[1] 29:12</p> <p>pituitary ^[2] 187:11 225:7</p> <p>pivotal ^[1] 76:1</p> <p>PK ^[1] 250:10</p> <p>place ^[5] 151:2 154:17 353:8 369:22 376:9</p> <p>placebo ^[156] 21:10 28:3 74: 22 75:4,11,12 76:22 77:11 79:12,13 80:3 82:5,17 83:6, 10,15 84:12,19 85:1,4 86:2,3, 6,21 87:2 88:3,9,19 89:16,20, 22 90:14,17 91:11 95:20 96: 7,13,15 97:18 98:17 100:4 103:22 104:4,12 105:18,20 106:18,20 107:3,16,21 110: 11,21 111:4,14,14,15,18 112: 1,2,5 113:15,19 115:7,8,15, 18,19 116:7,8 120:8,17 122:5, 21,21 124:11 125:5,15,17 126:3,12,14 127:2 130:17 131:2,6,19,22 132:5,6,14,16, 17,18 133:5,15 135:14,15 174:22 175:13 176:16 177: 12,17 178:22 179:3,21 226: 21 227:9 252:10,11,15 253: 12 257:18,19 259:6,13 261: 12,20 262:10,15 263:9,15 264:4 267:20 271:2,17 272:5,</p>
---	---	---	---

<p>12,14 275:18,21 277:3,7,17 280:19 281:9,12 282:13 283: 21 284:13 285:5,15,21 286: 18 288:13 289:14 290:6,11 292:22 313:19 319:3 330:17 340:14 341:19 344:5 359:11 placebo-adjusted [3] 80:1, 20 81:11 placebo-controlled [4] 76: 16 114:18 115:18 116:12 placebo-treated [1] 261:14 placed [2] 281:14 287:22 Plan [24] 3:21 11:16 36:2 44: 16,19 46:2 48:21 89:14 140: 4 141:19 142:11 145:14,18, 18,19 148:3 151:21 159:13 168:19 212:19 262:8 263:4 327:22 334:8 planning [1] 30:19 plans [1] 367:10 plaque-like [1] 218:1 plaques [1] 13:18 plasma [4] 198:22 208:8 220: 19 248:9 plastic [1] 162:22 plateauing [1] 373:18 plausibility [1] 362:9 plausible [7] 27:13 65:7 213: 18 269:1 274:9 292:8 361:7 play [2] 207:13 261:6 player [1] 61:14 players [3] 164:1,12 186:16 please [16] 12:12,20 13:8 95: 15 118:22 177:6,19 178:17 303:22 324:12 327:7 329:2, 12 340:5 345:6,7 pleasure [4] 49:2 150:5 157: 19 235:8 pleiotropic [4] 195:14,16 199:13 203:17 plot [2] 264:12 265:9 plus [3] 162:4 171:1 338:19 podium [1] 180:18 point [43] 12:7,11 41:17 60:13 80:16 108:1 113:5 117:14 138:5,16 143:22 177:10 181: 11 182:2 183:1,6 219:12 222: 8 250:11 252:16 257:2 258:6 263:16 265:14 275:19 285:6, 17,19 286:7,8 290:14 309:12 311:6 329:2 344:18 345:4 347:15,16,21 350:19 379:9 382:2 384:22 pointed [3] 312:21 337:8 370: 16 points [10] 49:20 81:17 134: 15 158:16 179:14 203:15 211:4 228:10 310:2 370:13 polymorphism [1] 63:1 pool [1] 363:8 pooled [6] 32:16 170:18,21 275:15 277:3 334:18 pools [1] 95:8 population [54] 11:5 35:9,21 38:13 62:11,21 63:3 69:22 78:10 79:1,3,5,7,8 81:6,7 82: 11,15 83:12 85:21 86:15 95:</p>	<p>10,18 99:10,14,14 100:9 110: 14 114:12 121:22 137:4 170: 22 179:20 227:18 228:2,8,13, 14,16,22 244:15 255:6 256:1 282:10 289:2 298:6,11 311:8 312:9 321:3 322:16 323:5 343:5 365:7 populations [7] 94:13 114: 14 129:15 256:7 312:11 314: 3 356:19 PORSHAN [1] 181:16 portion [1] 228:9 positional [1] 303:15 positive [9] 146:22 159:22 160:5 169:18 170:3 171:4,13 237:20 370:8 positives [1] 20:16 Posner [26] 3:10 9:11,12,15 11:7 14:19 15:2,7 33:16,18, 21 34:12 35:2,10,22 36:9 45: 22 98:10 108:14 109:14 110: 3 113:10 121:5 122:13 135: 21 136:10 Posner's [4] 282:22 283:2,12 372:14 possess [1] 269:10 possibility [10] 108:15 162:1, 2 268:22 291:9 300:13 304: 21 341:4 350:15 357:5 possible [34] 21:8 28:19 110: 3 113:2 131:7,8,13 132:3 133:2,11,15,19 146:9 157:15 163:14 165:14 167:15 173:6 199:2 228:10 246:12 279:1 283:8 297:17 307:16 317:20 320:18 363:10 367:9 369:18 370:7 372:16 376:18 378:13 possibly [10] 79:14 101:18 110:4 111:6 207:18 242:3 283:15 288:20 335:2 385:12 post [1] 362:13 post-approval [1] 215:7 post-death [1] 218:2 post-traumatic-stress [1] 273:15 posted [1] 230:12 postmarket [1] 117:11 postmarketing [25] 40:16 45: 17 120:3 121:14 127:9,11 134:22 139:7 143:4,6 165:19 182:10,19 215:11 240:21 241:4 267:13 268:1 286:15 287:9 296:11 327:21 368:21 369:2 376:20 postsynaptic [2] 192:19 193: 2 postsynaptically [1] 192:16 potassium [1] 195:2 potencies [1] 55:6 potent [1] 43:2 potential [26] 24:1 41:6 49:18 57:22 127:13 128:8 129:21 140:12 147:4 154:7 157:8,10 165:16 170:4 230:16 243:21 269:5,8 270:10 273:1,3 298: 8 320:6 326:10 355:8 364:6 potentially [5] 21:14 119:18</p>	<p>199:2 282:10 367:11 potentiates [1] 210:8 potentiation [9] 210:13,17, 18 pound [1] 75:15 pounds [23] 71:10,12 75:3,17 77:22 80:4,12,14,15,17,21 81: 8,9 84:11,12 88:8,8 174:17, 18 333:15 353:16 361:20,21 Practical [1] 158:6 practice [3] 159:6 166:11 314:10 pre-clinical [1] 269:3 pre-diabetes [1] 73:1 pre-diabetic [1] 78:21 pre-existing [1] 128:21 pre-synaptic [1] 269:16 pre-treatment [1] 228:6 preceded [1] 77:1 preceding [1] 67:1 precise [1] 26:14 precision [1] 265:13 Preclinical [13] 3:27 11:19 50:5 63:5 134:2 185:5,14,18 230:11,14 246:16 269:20 272:17 preclude [2] 8:17 223:16 precursors [1] 51:2 predict [2] 317:14 368:13 predicted [2] 107:4 297:2 predicting [1] 52:2 predictive [2] 31:8 280:11 predisposition [1] 274:12 predominantly [7] 198:8 219:22 255:7 262:13 263:14 264:6 282:3 preface [1] 184:21 preferential [1] 355:11 preferred [11] 17:21 262:7 263:2 264:1 276:10,13 278:6 293:14 302:13 304:13 306: 11 preformed [1] 51:2 prefrontal [1] 273:17 prejudice [1] 236:2 premature [1] 98:5 prep [1] 352:8 preparation [2] 22:6 48:10 preparations [2] 161:13 218: 19 preparatory [1] 285:3 prepared [5] 109:5 150:15 283:12 299:21 313:13 Presbyterian [1] 158:1 prescribe [1] 73:21 prescribed [9] 76:18 118:15 144:16,20 152:22 156:8 232: 15 273:10 293:13 prescribing [3] 144:14 147: 19 356:9 prescription [13] 71:18 142: 8 143:16 144:8,12 147:11 153:12 154:2,12 156:3 229:9 352:2 363:5 presence [9] 57:11 73:4 190: 13 201:20 202:3,7 270:13,15 274:14</p>	<p>present [27] 13:17 14:2,20 37: 3,20 39:5 50:2,4 51:22 67:3 69:4,12,14 79:2 87:15 93:11 97:8 177:4 185:20 191:15 192:15,16 261:5 268:13 310: 19 335:15 354:21 Presentation [34] 3:9,11 10: 11 11:17 12:1 14:20 15:3 36: 12,13,15 37:12 44:8 53:13 79:18 93:17 98:10 138:9 158: 14 170:8 185:11 186:2 187: 13 197:8 200:12 207:7 222:8, 22 223:19 224:3 250:18,20 251:7 300:4 321:5 PRESENTATIONS [6] 3:26 4:13 11:7,15 185:17 368:16 presented [26] 35:6 37:17 58: 21 77:13 78:15 80:6 82:6,8 117:22 139:11 204:10 229: 17 242:14 310:7,10,17 327: 16 329:21 333:6 334:7 358: 18 360:2 364:5,21 367:8,14 presenting [1] 251:12 presents [1] 271:21 preserves [1] 254:22 President [5] 36:22 69:2 93: 3 158:8 327:12 prespecified [2] 89:13 348: 12 pressing [1] 159:14 pressure [10] 162:3 164:12, 20 234:3 241:11,13,20 242:4 253:15 298:22 pressures [1] 236:3 presumably [3] 60:16 331:5 361:16 presynaptic [2] 193:6,11 presynaptically [1] 192:15 pretty [5] 343:18 352:13 358: 5 359:19 361:4 prevalence [7] 33:6 35:15 78: 5 171:16 255:22 330:5 371: 21 prevalent [1] 356:14 prevent [5] 57:17 72:16 163: 21 169:15 322:16 Prevention [7] 7:21 41:7,14 72:18 94:14 169:4 238:14 prevents [1] 54:4 previous [17] 10:5 26:18 105: 13 109:17 114:1 115:5 128:4 149:9 150:21 194:21 208:16 249:19,21 341:9,12,15 368: 12 previously [3] 8:9 41:19 88:2 prey [1] 237:8 primarily [1] 61:20 primary [17] 21:19 22:2 23:5 50:12 62:13 80:2,21 141:1 149:12 259:12,15 260:9 276: 8 284:11 299:10 302:14 365: 15 primates [1] 202:19 primers [1] 66:17 principle [1] 349:6 prior [11] 26:15 117:20 118: 10 128:11,21 148:2 150:9</p>
--	---	---	---

<p>154:2 184:18 270:17 275:1 priori ^[1] 52:2 privilege ^[1] 369:15 proactive ^[1] 367:10 proactively ^[1] 353:5 probability ^[1] 193:12 probable ^[1] 228:10 probably ^[14] 130:2 172:7 247:5 248:7 270:7 297:8 302: 7 315:22 319:17 335:4 341: 11 358:8 363:12 381:13 probes ^[1] 30:11 problem ^[19] 16:9 19:16 29:2 30:10 134:3 157:17 173:21 229:15 237:7 239:12 302:17 303:1 316:16 319:15 330:11 332:19 350:18 360:10 382: 11 problematic ^[1] 52:3 problems ^[10] 19:6 161:6 231:10 244:10 245:12 317: 15 330:10 331:17,19 340:17 procedure ^[4] 43:14,21 45: 18 80:18 proceed ^[3] 309:19 349:13 370:8 proceeding ^[1] 355:20 proceedings ^[2] 5:17 221:7 process ^[14] 145:16 146:10 168:18 192:12 222:17 246:5 267:9 271:7,15 299:19 302: 21 322:20 374:14 376:2 processes ^[4] 51:11 59:8,17 188:15 produce ^[1] 194:5 produced ^[1] 152:3 produces ^[1] 162:16 producing ^[1] 233:21 product ^[15] 9:9 11:3,4 43:20 44:5 95:6 141:11 142:21 151: 11 155:5,9,18 157:16 223:5 252:20 production ^[1] 88:15 productive ^[1] 50:15 products ^[10] 9:20 10:6 71: 14 74:6 175:5 185:16 243:17, 19 246:7,11 profession ^[1] 243:3 professionals ^[2] 141:10 152:1 Professor ^[5] 6:20,22 49:3 157:21 303:6 profile ^[27] 12:20 13:3,11 21: 13 94:2 98:4 106:6 134:17, 22 135:11 137:9 138:13,16 139:9,12 155:19 168:16 199: 8 214:14 230:4 276:3 308:18 335:20 337:16 342:14 366:8 383:16 profiles ^[1] 165:17 program ^[42] 39:9 40:7,8,10 72:18 75:19,22 84:8 93:13, 18 94:12 95:17 97:10 99:18 100:6 103:3 109:3 116:2 119: 11 134:18,19 141:17 142:9, 18,20 143:2 151:6 154:12 155:2,10 158:1 168:3 169:4</p>	<p>204:8 230:15 238:14,19 322: 7 327:20 328:1 333:15 335:2 programme ^[1] 215:8 programs ^[3] 93:19 100:12 244:17 progress ^[4] 153:20 154:4,19 336:13 progression ^[2] 117:19 267: 8 progressive ^[2] 118:18 208: 18 progressively ^[1] 85:2 project ^[1] 95:3 proliferation ^[1] 356:18 proline ^[1] 62:14 prolonged ^[4] 181:8 270:15 274:19,22 prominent ^[2] 53:7 59:17 promotes ^[1] 61:10 promoting ^[1] 267:10 prompting ^[1] 291:3 prone ^[1] 216:4 pronounced ^[1] 297:22 prove ^[1] 383:3 properly ^[2] 155:19 373:4 properties ^[5] 50:1 88:21 225:19 269:11 272:16 property ^[1] 55:7 proportion ^[5] 177:13 252:12 328:8 340:12 363:4 proportional ^[2] 174:15 175: 8 propose ^[1] 310:18 Proposed ^[13] 3:21 11:16 42: 7 74:16 85:14 92:19 126:19 136:10 198:1,11 205:9 211: 16 213:13 proposing ^[2] 46:2 140:5 pros ^[1] 367:22 Proschan ^[18] 2:9 7:18,18 33: 19 180:9,10 181:2 315:6 316: 10,16 323:22 325:12 359:3,3 372:13 378:18 384:11,12 prospective ^[7] 16:4 27:22 29:6 32:10 241:15 373:8 377: 1 prospectively ^[5] 98:11 101: 15 136:8 375:5,6 protect ^[1] 246:6 Protection ^[1] 119:10 protective ^[1] 274:2 protein ^[3] 42:18 64:21 195: 20 proteins ^[2] 53:6 188:15 protocol ^[4] 78:17,20 180:19, 22 protocols ^[1] 180:19 provide ^[7] 57:2 142:2 144: 16 147:10 153:4 215:3 374:2 provided ^[5] 153:15 155:6 250:17 258:21 271:15 provider ^[5] 27:19 141:6 149: 13 159:9 166:12 providers ^[3] 142:10 168:4, 21 provides ^[6] 65:6 74:9 97:18 248:4 256:17 264:12</p>	<p>providing ^[5] 5:9 37:9 50:5 150:16 151:12 provoke ^[1] 34:22 proximal ^[1] 304:4 PSUR ^[1] 45:19 psych ^[2] 295:14,17 psych-related ^[2] 295:12 296:8 psyche ^[1] 340:16 Psychiatric ^[75] 9:13 12:13 14:22 45:21 98:19 99:5 100: 7 101:4,20 102:14 117:22 120:19 122:8 123:2 167:8 173:5 226:8,11 228:2 239:16 251:21 258:14 260:6 273:5 274:5,15 276:3,9 277:2,7,15 278:4,11 279:16,21 280:6,14, 16,20 281:22 282:7 291:6 293:7 296:4,4 297:12 307:17, 22 310:13 313:9 317:13,14 318:4,7,10,13,15 329:3 340:9 343:10 344:3 347:3,10 349: 19 350:9 355:1,14 356:13 358:3 368:12,15 369:1 373: 21 374:8 378:2 psychiatric-disease ^[1] 317: 12 psychiatrist ^[3] 118:4,14,16 Psychiatry ^[8] 7:9,17 9:14 14: 22 16:10 25:6 48:18 322:4 psychoactive ^[1] 50:12 psychological ^[1] 313:5 psychomotor ^[1] 319:11 psychosis ^[3] 274:7 313:1,17 psychotic ^[5] 274:1 312:20 313:14,22 350:16 PTZ ^[2] 210:19 216:1 Public ^[20] 4:2,4 8:11 11:22 69:18 91:8 185:8,9 221:5 222:3,14,16,19 223:2 224:2 237:16 239:11 250:16,17 251:3 published ^[5] 8:10 42:3 49:6 225:17 234:9 pulls ^[1] 24:2 pup ^[1] 231:6 purely ^[1] 63:18 purpose ^[1] 259:4 purposes ^[1] 257:14 pursue ^[1] 355:3 put ^[16] 22:9 30:12 57:5 124: 20 137:8 157:2 182:4,6 184: 5 316:6 327:15 333:12 365: 14 368:14 378:14 380:6 puts ^[3] 24:2 81:3 163:13 putting ^[1] 145:21 pyriform ^[1] 225:3</p>	<p>quandary ^[1] 356:5 quantify ^[2] 342:11 348:5 quarter ^[6] 78:22 104:3 320: 19 321:1 333:3 363:4 queried ^[2] 149:7 313:4 queries ^[2] 182:1 313:5 query ^[4] 337:13 338:15 340: 1 351:17 querying ^[2] 306:22 342:13 question ^[57] 12:17,22 28:22 34:6 36:6 60:17 102:8 121:9 149:8,21 165:15 171:8,12 172:11 173:9 174:2 175:6,20 176:4,9 180:2,9 181:15 184: 19,22 216:21 227:22 299:14 304:1 311:17 314:8 315:5 317:12 321:12 322:22 323:9 325:21 326:2 328:21 330:9 333:19 335:17 336:4 338:16 340:8 345:7,12,19 349:10,11 353:20 358:17 372:5,19 375: 17 383:12,13 questioned ^[2] 127:1 288:12 questioners ^[1] 184:15 questioning ^[5] 95:1 98:7,8 102:1 303:20 questionnaire ^[6] 102:17 120:20 121:5,10 136:8 150:3 Questions ^[53] 3:25,29 4:16 12:8 30:11 33:18 35:1,18 36: 7 37:7,10 130:9,10 135:10 139:22 167:18,19 170:11,14, 15 174:14 175:3 185:7 215: 15,17 216:11 217:19 219:11 220:21 222:11 230:5 231:22 237:17 249:8 250:10 288:19 299:22 300:1,3 301:1,9 312: 8 317:9 321:14 322:22 326:1 327:4,5 328:16 354:9 355:7 357:11 371:17 quick ^[1] 261:1 quickly ^[1] 157:15 quit ^[2] 114:21,22 quite ^[7] 86:8 227:11,14 352: 9 356:14 375:20,21 quote ^[1] 215:3 quoting ^[2] 309:2 339:3</p>
--	--	---	---

R

R ^[3] 5:1 222:1,1
R&D ^[1] 8:6
rabbit ^[1] 212:22
rabbits ^[4] 204:22 205:16
231:7 323:19
race ^[2] 86:9 255:15
radiolabeled ^[1] 220:18
radioligand ^[1] 198:20
raise ^[1] 106:22
raised ^[7] 126:8 130:10 227:
22 329:2,8 355:6 382:8
raises ^[2] 232:5 375:16
raising ^[1] 242:8
ramifications ^[1] 347:5
random ^[3] 264:16 278:7 359:
15
random-effects ^[1] 260:7
randomization ^[17] 97:17
110:19 230:7 255:1 256:12

Q

qualified ^[1] 79:6
quality ^[27] 70:12 72:13 90:20
91:10 92:14,15 161:7 165:6
168:14 170:18,20 171:9 172:
9,18 173:2,6,11,21 177:21
178:4 230:6 244:7,18 342:17
357:21 358:22 375:14
quality-of-life ^[3] 357:11,19
358:18

260:8 272:9 277:11 284:11, 14,17,18 285:16 286:9,10 317:2,5 randomizations [4] 77:1 259:18,21 260:11 randomized [13] 76:15 96:13 109:9 110:19 114:21 121:20 129:12 226:10 254:12,20 259:8 284:10 339:17 range [10] 32:4 57:5,6 72:9 77:21 126:15 160:4,8 227:5 229:18 ranged [3] 254:1 259:9,11 ranging [1] 11:15 Raphael [1] 50:13 rapidly [1] 188:10 RAPSODI [1] 41:13 rare [5] 95:10 115:10 129:13 136:1 260:1 rarely [1] 137:17 rarity [1] 110:6 rat [17] 66:20 68:13 198:22 204:15,16,17 205:22 206:6 208:20 209:9 212:21 220:17, 19 247:13 248:2,5 360:3 rate [35] 35:15 78:6 81:22 82: 3,14,17 83:17 115:20 116:6,9 117:5,7 121:21 126:15,20 131:16,18 171:1,5,15 174:12, 13,21 175:14 229:16,22 253: 22 255:17 272:3 290:1,5 340: 11 359:6 362:10 366:18 rated [1] 127:15 rates [21] 79:9 122:11 125:16 136:3 171:10 175:7,10,11,19, 20,21 176:2 230:9 253:20 254:5,13 257:13 261:10 290: 8,14 369:1 rather [11] 51:1 52:3 73:14 142:19 160:21 206:19 207:4 315:18 331:3,11 343:12 Rating [3] 28:10 29:5 34:3 ratings [1] 26:16 ratio [22] 25:18 77:19 86:9 114:7 116:15 132:7 234:15, 20 259:17 285:20 286:11 315:19 317:2,5 324:10,18 325:3,5,6,9 367:5 374:7 rational [1] 164:9 rationale [2] 50:5 255:1 ratios [2] 270:7 290:3 rats [18] 65:13,19,19,21 66:9, 11,12,13,17 204:13,22 209: 17 231:13 248:2 269:22 270: 4 323:19 360:4 re-evaluation [1] 156:21 re-implementation [1] 146: 9 re-operation [1] 163:5 re-randomization [5] 39:4 77:8 96:6 258:4,5 re-randomized [12] 77:10 84: 17 96:19,21,22 97:3 110:21 115:3 254:2 257:17 277:10 284:8 reach [2] 252:12 349:4 reached [3] 102:6 144:2 336:	20 reaching [5] 80:16 81:7 85:2 87:1 304:5 reacted [1] 144:22 reaction [1] 71:3 read [5] 5:12 130:2 182:11 222:15 230:21 readily [2] 147:6 200:16 reading [2] 250:21 352:8 reads [1] 12:22 ready [1] 91:15 real [11] 17:11,13 160:19 165: 7 237:16,22 240:4 296:3 300: 16 350:4 356:5 realistic [2] 72:3 148:4 realistically [1] 154:20 reality [3] 362:19 376:14,15 realize [5] 55:4 328:13 363:9, 10,16 realized [1] 315:17 really [68] 16:17 18:16 20:19 23:12 25:18 26:3,10 30:1 50: 10 104:11,19 123:16 124:19 136:13 174:11 179:15,18 185:4 196:3 220:3 235:19 236:9,13 237:8 238:11,12,18, 20 239:8,9,12 241:3,5,17 242: 4,6,15 243:4 265:13 279:6 285:18 292:15 296:2 297:19 310:9 324:21 332:6,14 334: 20 345:12 349:21 351:2 352: 9 362:14 363:9 370:15,21 371:20 372:4,17 376:22 378: 4,11 379:15 381:4,7 382:4,11 reappears [1] 85:9 reason [13] 26:11 28:21 29: 15 71:5 111:22 126:3 223:1 256:14 274:10 287:6 288:8 355:7 363:19 reasonable [3] 258:18 334:2 372:2 reasoning [2] 326:18 349:5 reasons [13] 12:15 82:14 115: 9 136:4,15 175:16 253:14 329:6 340:11 361:22 362:21, 21 363:2 reassess [1] 282:18 reassessment [1] 148:7 reassurance [1] 215:4 reassuring [2] 134:11 235: 18 rebutting [1] 347:19 recall [1] 290:8 recalls [1] 155:17 receive [3] 47:2,21 303:9 received [14] 96:4,11 102:13 118:8 243:13 257:20 267:15, 16 268:2 293:22 309:9,14 311:18 338:4 receiving [9] 48:5 117:13 139:17 140:12 229:7 267:18, 19 277:4 298:6 recent [5] 61:12 120:5 224:15 225:11 234:8 recently [11] 39:14 45:16 46: 9 58:21 73:22 118:8 145:11 156:8 189:2,6 288:15	receptor [51] 11:1 42:4 51:16 52:2,12,17 53:4,11 54:5,18, 20 55:15 59:14 68:5,15 164: 11,12 190:7,13 191:8,9,19 194:18,18 196:21 197:5,17, 19 198:4,7,9,12 199:22 201:6 203:1,16,22 204:2 207:20 211:12,19 213:16 214:11 224:11 233:7,8,20 267:6 274: 8 292:10 366:2 receptors [70] 49:7 50:16 51: 6,19 52:9 53:1,3,8,13,16 56: 4,6,8,12,20 57:8,17 59:9,13 60:4,6,7 164:7 188:21 189:1, 4,9,10,11,16,17,22 190:11,20 191:3,6,14,14 192:5,15 193:3, 6,7 195:6,7,8,9,10,11,12,12 196:2,9 197:10,11,13 198:14 199:2,5 200:21 201:11 202: 18 203:21 207:11 211:8 224: 21 226:7 269:17 273:16 371: 2 recessed [1] 221:8 recognize [5] 163:19 245:16, 17 327:6 356:6 recognized [3] 74:10 88:20 147:5 recognizing [1] 343:11 recommend [3] 33:20 108:2 137:5 recommendation [1] 102:11 recommendations [3] 5:14 76:20 382:13 recommended [6] 39:22 47: 9 109:16 150:9 232:3 244:17 recommending [4] 29:16 47: 20 141:4 150:13 reconcile [1] 357:15 reconciliate [1] 180:3 reconfirmed [2] 127:10 336: 17 reconvene [4] 184:10,12 221: 5,8 record [2] 8:17 10:2 recorded [7] 104:2 110:17 281:17 306:5,7 321:9 371:7 recording [1] 276:5 recover [1] 379:18 recovered [6] 107:11 113:17 266:9,12 280:20,22 recovering [1] 280:20 recovery [5] 104:8 123:15 135:16 186:21 225:14 recruited [1] 100:16 recurrent [1] 274:18 red [2] 65:19 291:14 redesigning [1] 382:6 reduce [9] 161:9 168:15 169: 8 252:22 267:4 322:13,16,19 363:21 reduced [4] 26:17 68:9 209: 12,14 reduces [3] 164:11 244:8,18 reducing [8] 87:10 88:11 138: 18,19 267:9 297:5 298:19 312:22 reduction [16] 63:6,9 64:4 83:	9,11 87:4 88:5 92:4 140:16 145:9 160:13 234:2 346:14, 15 348:18 360:22 reductions [1] 253:14 redundant [1] 163:20 Redux [6] 224:16,18 236:15 237:3 240:22 242:15 reeducate [1] 145:2 refer [1] 93:21 reference [2] 57:2 150:4 referenced [1] 41:9 referred [1] 167:18 referring [1] 380:12 refers [3] 108:17 196:19 208: 13 reflected [1] 228:1 reflective [1] 220:12 reflects [2] 201:9 366:8 refrain [1] 5:17 refreshing [1] 330:6 regain [1] 85:10 regained [2] 85:2 232:13 regard [8] 203:1 230:7 251: 13,17 253:19 298:21 340:17 349:10 regarding [6] 12:12 215:4 270:9 314:8 329:3 340:8 regardless [3] 181:3 271:7 279:6 regional [2] 190:10 202:22 regions [5] 190:13,19 191:7, 17 225:3 registration [2] 95:6 162:21 registry [1] 144:4 regression [10] 89:10,17,21 90:3,8,11,15 331:22 348:12 360:11 regularly [1] 102:4 regulated [2] 9:4 52:13 regulating [4] 163:20 207:14 269:12 366:4 regulation [16] 164:2 186:19 187:15 189:18 199:14 200: 22 201:11,21 203:20 207:18 213:17 214:18 225:21 231: 16 269:17 273:19 regulators [2] 165:12 215:2 regulatory [5] 43:10 187:8 190:14 276:7 293:15 reimbursement [2] 240:16 303:9 reinform [1] 145:1 reintroduce [1] 223:20 rejection [1] 234:18 relapse [1] 94:14 relapses [1] 129:1 related [15] 53:3 66:17 69:12 70:7 108:16 174:14 210:14 229:4 234:5 239:10 244:12 329:10 332:2 366:13 378:18 relates [2] 170:17 171:12 relationship [18] 11:11 16:22 32:12 69:15 89:2,5,11,15,19 122:14 137:19 159:22 160:5, 5 164:6 182:17 223:4 344:14 relationships [2] 223:13,14 relative [38] 99:14 131:22
--	--	--	---

<p>132:19 133:8 175:4 179:1,2 198:22 207:3 208:5 213:1,5 220:19 222:9 247:1,17 249:1 250:1 253:1,12 259:16 264: 13,21 265:10 272:5 278:3,6, 11,15,15,17,21 279:3,5,14 291:12 293:1 307:20 relatively [7] 53:2 62:21 191: 7 260:1 279:10 298:5 343:4 release [5] 58:6,9 193:8,9,13 released [2] 193:5 267:8 relevance [6] 186:10 203:4 212:18 214:7 235:1 369:19 relevant [15] 50:1 57:22 59: 18 68:3 137:12 199:20 203: 12 214:20,21 217:5 248:8 266:4 271:12 299:15 326:15 reliability [1] 25:20 reliance [1] 298:17 relied [2] 26:5,16 rely [1] 215:6 remain [4] 231:22 272:12,22 380:4 remainder [1] 207:7 remains [3] 268:21 282:8 298:15 remarkable [1] 300:8 remarks [2] 37:13 235:16 remember [8] 25:8 33:3,8 118:22 184:21 308:5 333:5 380:20 remind [7] 12:7 84:16 153:3 285:12 294:15 328:17 330:4 reminder [2] 153:6 261:1 reminds [1] 365:9 remodeling [1] 59:20 remote [3] 184:16 223:21 383:8 removal [1] 316:19 remove [2] 316:17 325:5 remyelation [1] 267:10 renal [2] 65:16 66:18 rental [1] 236:8 Rep [1] 8:7 repeat [5] 122:6 136:7 311:16 345:6 383:13 repeated [1] 134:5 repeatedly [1] 278:1 repeating [2] 343:20,22 replicated [1] 84:15 Report [1] 45:19 103:19 104: 3 130:15 136:1 146:7 182:10 266:18 268:4 288:11 319:6 reported [58] 8:20 17:4 91:9 99:20 101:8 107:8 113:6 117: 1,2,9,11 121:19 122:19,20 125:9 126:5 127:13 129:21 131:4 133:3,11 135:12 137:9, 17 143:3 166:21 175:5 196:6 215:11 220:18 233:5 256:20 262:2 266:8,10,12 268:5 270: 22 271:3 272:11 275:21 277: 7 280:19,22 282:14,17 286: 14 289:6 293:14 296:11 297: 20 302:18 319:22 320:14 334:13 341:17 351:15 362: 11</p>	<p>reporter [1] 127:16 reporters [1] 184:16 reporting [8] 288:17,21 289: 2,4 290:13 306:16 327:21 386:1 reports [12] 9:15 102:21 124: 4 182:12 215:12 258:19 268: 1 327:18 328:2,3,4 349:19 represent [8] 9:6 39:8 79:22 80:8 244:13 300:9 356:15 358:1 Representative [5] 2:19 7: 11 9:3 14:5 323:4 representatives [1] 145:1 represented [7] 20:16 40:4 41:15 42:14 78:22 83:15 90: 14 representing [3] 71:12 243:8, 11 represents [2] 164:21 264: 16 repro [2] 323:15,17 reproducible [1] 25:22 reproduction [2] 231:3 368: 7 reproductive [4] 204:21 225: 8 230:11 323:19 reptiles [1] 202:20 request [4] 12:11 79:13 176: 3 184:14 requested [4] 93:19 108:22 143:8 282:21 requests [1] 175:17 require [6] 104:7 125:4,11 307:2 346:2,5 required [16] 103:2 107:13 163:4 180:21,22 181:7 227:1, 12 232:5 234:14 273:8 281:7, 10 290:18 309:13 352:11 requirements [1] 95:5 requires [3] 158:18 234:17 252:17 requiring [2] 145:19 146:19 requisite [1] 336:15 RESEARCH [18] 1:3 4:5 7:14 9:16 15:17 16:15 23:15 34: 22 50:9,15 158:4 189:3,17 220:9 224:2 233:12 363:3 371:5 research-supported [2] 19: 22 23:17 researcher [1] 224:6 resistance [1] 67:17 resolved [2] 128:5 281:1 resort [2] 71:20 74:6 respect [5] 10:3 170:20 278: 21 340:15 341:21 respectively [1] 278:16 respiratory [1] 226:4 respond [2] 82:16 90:1 respondent [1] 82:3 responders [3] 82:8,15 279: 4 response [15] 45:12,14 46:11 54:8 55:8 57:13 81:22 176: 22 181:15 196:7 202:10,16 279:7 303:4 320:10</p>	<p>responses [2] 191:13 226:3 responsible [3] 241:3 261: 18 361:9 responsive [1] 363:7 rest [6] 41:12 44:21 304:7 341:22 353:20 369:5 resting [1] 55:1 restless [1] 263:17 restricted [1] 70:14 restriction [1] 66:1 restrictively [1] 192:8 result [9] 5:14 23:20 164:14 181:19 197:6 200:10 202:1 213:15 317:17 resulted [2] 19:10 286:10 resulting [6] 43:2 196:22 198: 6 199:15 205:15 269:16 results [30] 26:9 29:9 37:3 62: 17 64:2,17,19 69:12 72:19 75:18 79:20 80:1,20 81:16, 17 83:2 84:1 90:20 109:12 111:3 127:14 171:4 205:1 210:6 259:22 267:5 285:11 298:15 317:18 380:8 retained [1] 96:10 retiring [1] 14:1 retrograde [5] 192:6,11 193: 14 194:13 239:7 retrospect [1] 371:14 retrospective [6] 102:9,19 109:12 124:5 321:8 375:7 retrospectively [3] 110:15 260:19 271:10 return [2] 153:18 177:20 returning [1] 63:7 reuptake [2] 183:12 188:11 reveal [1] 289:17 revealed [6] 118:16 266:17 275:12,16 282:16 317:2 reveals [1] 281:16 reverse [2] 54:8 233:22 review [30] 36:8 37:14,18 43: 9 46:3,5,13 98:3 100:21 101: 9 117:16 119:17 123:22 124: 3 127:5 140:3 146:2 225:11 234:8 246:3,9,20 260:14 265: 22 281:15 282:14 299:18,19 300:1 323:20 reviewed [13] 45:10,20 48:21 94:7 121:12 130:7 131:12 132:3 146:8,8 245:21 289:17 373:5 reviewer [3] 6:13 8:1 282:16 reviewing [4] 38:22 40:11 69: 11 166:13 reviews [1] 283:4 revision [1] 145:20 revisit [1] 55:12 reward [1] 261:5 Rezulin [2] 224:16,19 RFMH [1] 15:19 Richard [3] 3:13,22 36:21 right [42] 19:1 28:21 30:4,12 47:1,11 48:1 53:7 64:14 71:8 75:6 83:8 87:5 90:3,15 107: 22 131:2,17 139:13,18 149:2, 8 157:7 167:19 173:19 179:5</p>	<p>222:7 237:15 240:19 241:22 250:9 302:16 308:5 313:15 314:2 315:3 325:12 353:5 354:19 379:9 381:10 382:22 righthand [1] 6:1 rigorous [3] 234:13 243:19 246:3 rimonabant [389] 1:5 3:17,19, 23,27 4:14 10:22 11:11,20 12:4,13 13:2 37:4,21 38:2 39: 1,21 40:14 41:5 42:1,2,13,16, 22 43:3,5,10 44:20 45:4 46: 22 47:1,2,3,10,12,21 48:10, 18 49:9,17 50:1,6 51:16 52: 16 53:1,9,14,18 56:1,11,15, 19,21 57:3,7,21 58:10,22 59: 2 60:20,21 61:2 63:7,15 64:3, 10,16,19 65:8,20,22 66:13,15, 20 67:5,5,16 68:4,8,12,18 69: 5,7 74:15,21 75:3 76:1,17 79: 11,16 80:4,13 81:5,14,18 82: 4,12,17,21 83:8,15 84:7,18, 21 85:10 86:3,5 87:8,22 88:9, 14,18 90:13,17 91:1,9,14 92: 3,8,19 93:7,12 94:2,10 100:3 101:2 103:22 104:5,12 105: 20 106:14,21 107:3,9,17,21 108:1 110:11 111:4,4 113:15, 20 116:19 117:13 118:9,14 120:10 121:2 122:4,16,20 124:10 125:1,5,6,14,16 126:1 127:13 128:2 131:5,19 134: 18 135:4,13 136:6 137:9 138: 14 139:8,14 140:10 141:2 144:9,14,16,20 145:4 147:10 148:13,19 150:10 151:8 154: 9 155:13 157:4 158:11,15 159:7,15 162:9 163:12 165: 17,18,21 166:5 168:7 169:5,8, 15,18 170:2 175:13,15 176: 16 177:11,15 178:5 179:5,7, 22 182:22 185:6,18,22 187:6 190:6 196:15,16 197:5,16,18 198:1,2,18 199:3,9,15,21,21 201:7,20 202:3,7,15 203:6,16 204:2,19 207:15 209:18 210: 4,7,22 211:7,8,10,14 212:5 214:10 215:6 216:8 217:7 220:4,11,14,18 224:14,22 225:20 226:20 227:1,10 228: 3 229:13 230:16 231:20 232: 9,12,18 233:1,8,15 234:9 246: 4,16 251:8 252:4,19,21 253:5, 12 254:6 255:8 256:5,18 258: 10 259:5,13 261:12,20 262: 10,14 263:9,15 264:3 265:4 267:13,18 268:3,8,17 269:5,7 270:2,6,13 271:1,2,4,17,17 272:4,11,13,18 274:13 275: 17,20 276:4 277:1,17 280:12, 18 281:4,6,20 282:9 283:21, 21 284:13,22 285:3,21 286: 14,16,21,22 287:2,4,9,10,15 288:7,8 289:3,14 290:1,6,10, 16,18 292:22 293:10,14 294: 12,16 295:4,13,17 296:18 297:4,5,11 299:6 309:22 313:</p>
---	---	--	---

<p>18 314:17,22 317:15 322:6, 12 326:4 327:20 329:3,22 332:7 333:12 339:21 340:8 341:1,18 342:15 344:4,10 351:19 357:6 368:14 380:4 383:15 rimonabant's [9] 11:2 12:19 13:11 53:21 186:5 204:8 273: 1 277:6 298:21 rimonabant-associated [1] 253:7 rimonabant-treated [6] 98: 16 105:18 261:13 289:1,9 293:6 RIO [55] 75:22,22 76:4,14,15 78:10 79:5,7,20 81:12 83:16 84:7,8 86:11 90:9,21 96:19 101:16 103:3 109:2 170:18 174:13 177:12 180:20 229:5, 18 253:21,22 254:11 255:11, 12,16,17,17 256:14 259:18, 19 261:19 262:2 264:15,21 267:18,20 271:1 275:6,12 277:4 278:4 279:11 281:6 284:7 286:19 311:20 312:4 313:19 RIO-diabetes [15] 44:13 76: 11 77:2,15,20 78:18,21 85:16 86:1,17 87:12 95:16 99:18 265:7 300:16 RIO-Europe [9] 39:6 76:3,6 77:4,18 80:5 82:11 84:10,20 RIO-lipid [3] 76:4,8 83:2 RIO-lipids [6] 77:2,19 78:15 80:19 82:12 300:15 RIO-North [13] 38:22 76:3,6 77:7,18 78:1 80:5 82:11 84:8, 15 96:5 115:3 118:21 Risk [128] 3:21 11:16 26:14, 17 20 27:20 28:13 31:20 37: 21 41:7 44:15,19 46:2 47:5 48:20 70:7,22 71:20 72:8 74: 7 78:10 91:18,22 97:22 100: 17 107:20 131:22 132:7,8,19 133:8 134:12 136:17 137:2,2 138:19,21,21 139:2 140:4,7,9, 11,12 145:14,17 158:15 159: 4 160:1,12,13 162:8,18 165: 15 168:5,10,13,15,19 169:8, 10 236:20,21 237:1 240:5 244:9,19,22 259:15,16,17 264:13,21 265:4,10,15 269:5 272:5 273:1,3 278:3,6,11,14, 15,17,21 279:4,5,18 281:22 287:8 292:13,20 293:1,2 297: 2,12,14,18 299:8 300:12 307: 16 310:4,8,13,15 313:9 315: 18 324:3,10,18 325:12 327: 22 334:8 341:16 343:13 345: 17 348:19 350:21 351:1 352: 6 354:16,21 356:17,19 357:9 365:14 risk-benefit [6] 13:3,11 32: 20 44:20 297:3 308:18 risk/benefit [3] 355:5 374:7 383:15 risks [19] 140:10,16 141:1</p>	<p>145:15 156:18 157:10 159:8 166:15 170:4 224:11 238:5 258:9 297:10,21 298:1,1,9 307:20 355:13 RMP [7] 142:3 145:22 155:3 156:14,17,21 157:16 Road [2] 1:10 337:2 Robert [1] 2:16 robust [1] 25:21 Rockefeller [2] 6:21 329:15 rodents [5] 198:19 202:19 205:16 215:18 217:10 role [21] 9:5 61:6 62:9 65:5 164:2,13 178:6,7 179:6 186: 3,16 196:18 200:21 207:13 231:19 245:16 261:7 274:3 292:8 312:21 375:22 roles [7] 189:2,20 190:14 191: 22 192:1 225:13,15 room [7] 5:7,11,21 223:21 235:22 236:2 336:2 rope [1] 17:20 Rosebraugh [3] 2:25 6:4,6 Rosen [133] 2:2 3:3 5:3,5 7:4, 4 8:8 10:9,16 13:17 14:15 33: 16 34:8,20 36:7 170:9 173:9 177:18 180:8 181:13 182:3 184:9,12 215:14,16,22 216: 10 217:19 218:11 219:10,13 220:21 221:3 222:2,15 235:7 243:6 246:15,18 249:5,11 250:2,9 251:2,9 300:2,21 303:2,19 304:16 305:14 306: 22 307:14 310:1,20 311:14 313:11 314:7 315:4 316:17 317:8 320:2 321:6,10 322:2, 21 323:9,21 324:14 325:20 326:22 328:17 335:16,22 337:13,18,21 338:1,12 339:1, 11,22 340:4 342:13,18,22 345:3,8 346:18,21 347:14 349:14 351:17,21 353:22 354:2,6 355:21 356:3 358:11, 14,16 362:2 364:11 365:18 367:17 369:7,9,12 370:10 372:18 374:11 375:16 377:7, 11 378:8,17 379:9,22 380:11 383:4,21 384:1,1,4,7,9,11,13, 15,17,19,21 Rosenzweig [21] 3:18 37:17 39:5 69:2,4,6,8 93:1 96:5 111:20 138:18 147:22 171:6, 8,19 172:12 174:7 175:3,6 176:11 178:18 rough [1] 343:9 roughly [6] 254:12 280:5 281: 22 314:12,16 344:7 route [1] 355:19 routine [2] 141:8 142:1 routinely [1] 94:22 rubric [1] 305:3 rule [1] 292:3 run-in [7] 76:22 80:16 86:2,5, 11 130:17 132:14 running [2] 51:11 181:13 Ryder [7] 2:20 8:6,6 9:2,8 14: 5 369:11</p>	<p>Ryder's [1] 9:5 <hr/>S <hr/>S [5] 2:17 3:1 4:1 5:1 222:1 SAE [2] 180:16 181:18 SAEs [1] 181:17 safe [2] 215:5 245:20 Safety [102] 3:19 4:14 11:4 12: 3,19 15:6 18:14 26:13 28:3 29:8 30:13 31:14,15 32:18 37:19 39:18 40:2 41:17 44:8 45:14,19 46:21 47:10 49:18 79:18 93:7,12 94:2 95:1,7 96: 18 98:3 103:8 106:6 108:1 112:2 134:15,21 135:11 137: 9 138:6,13,16 139:9,12,21 161:18 165:11,17 168:16,17 208:1,12 215:6 218:17 222:6 229:21 230:1,4,10 232:7 234: 14 243:18 246:3 247:16 248: 12 249:20 251:8,13,19 256:2, 5 257:12 258:13 259:6 260:1, 4 269:3 270:8 309:4 327:13, 15 329:10 335:20 336:7 337: 16 342:14,17,19,20 349:12, 13 351:19 353:18 354:11 358:13 362:7 363:7 364:14 370:22 376:12 377:18 Sahlroot [4] 324:11,15,15 325:17 said [48] 18:13 20:19 22:14 23:16 26:8 27:5 29:17 30:22 31:9 35:22 77:1 98:6 108:21 120:3 130:22 139:15 146:13 148:12 150:11 225:12 229:2 230:10 232:16 237:22 306: 12 308:9 309:3 316:13 330: 11 336:14 337:19 338:7 339: 15 341:22 343:2 345:9,21 349:17 352:10,21 354:5 356: 2 358:10 362:17 364:18 365: 17 369:4 380:21 sales [1] 145:1 salivation [1] 183:4 same [64] 16:19,19 19:18 34: 2,6,6 44:1,1 45:5 63:20,21 65:21 68:18 79:21 86:10 87: 5,18,19 88:7 89:19 90:13,16 96:8 97:2 100:15 105:9 106: 21 132:7,13 133:12,12 139:1 142:9 163:11 164:10 165:8 166:18 170:22 175:13 176: 12 178:14,14 182:20 183:1 200:8 212:9 233:7,12 245:21 246:10 257:20 277:4 289:14 294:19 320:8 326:4 330:14 331:3 332:11 337:9 341:17 344:16 345:12 360:4 sample [4] 87:15 156:7 259:9 315:13 Sanofi [12] 11:14 37:1 216:8 230:13 262:7 263:3 269:4 282:17,21 283:12 299:4 302: 22 Sanofi-Aventis [15] 1:6 3:11 9:16 36:14,16 37:18 69:3 93: 5,15 121:4 140:5 151:6 172: 16 243:14 322:4</p>	<p>sat [2] 352:3 369:21 satiety [1] 52:6 satisfied [4] 143:13 181:14 252:8,19 satisfy [1] 319:8 satisfying [1] 381:6 Saturday [1] 380:22 saw [14] 20:17 42:14 82:10,21 84:20 105:13 122:12 132:13 133:4 167:7 236:14 300:17 322:18 360:5 say [32] 21:6 29:10 35:3 98:11 104:19 109:20 180:5 181:17 184:21 218:7 241:9 290:12 312:8 319:16 337:5 339:6 343:2,3 346:16 348:17 351:8 352:2 353:12 357:15 358:12 359:18 364:9 367:8 372:13 375:6,6 380:18 saying [3] 236:10 239:20 347: 11 says [8] 6:5 143:7 182:12 242: 2 309:14 349:4 374:18 384:1 scale [16] 16:4 23:11,14 28: 10 29:5 34:3 35:19 90:22 102:2,3,6,8 109:19 179:15 228:6,9 scales [4] 28:8 29:22 34:13 378:1 scan [1] 128:15 scant [1] 126:20 scared [1] 242:15 scary [4] 235:19 239:8 240:5 242:12 schedule [4] 12:5 36:11 153: 18 185:3 scheduled [1] 299:12 schedules [1] 5:8 schematic [2] 67:3 154:1 scheme [2] 21:19 77:8 schemes [1] 256:13 schizophrenia [7] 94:15 110: 8,13 114:12 129:16 274:3 312:14 schizophrenic [3] 274:1 285: 7 312:10 schizophrenics [2] 256:7 313:21 School [1] 7:9 science [1] 239:2 Scientific [3] 36:22 243:19 365:22 Scientist [1] 7:5 scientists [2] 231:19 245:15 sclerosis [16] 101:11 126:9, 11 127:2,11,14,16,19,22 128: 8 238:20 239:1,4 340:19,20, 22 sclerosis-like [1] 218:1 score [4] 91:1 228:9,11,12 scores [1] 228:7 scratch [1] 377:6 screen [1] 167:13 screened [6] 147:11 219:6 275:6 282:9 288:7 298:6 screening [9] 76:18 167:16 168:21 169:21 270:17 275:2,</p>
--	--	--	--

<p>7 317:12 368:13 scripted ^[1] 120:19 scripts ^[1] 314:12 search ^[5] 20:20 25:9 120:20 130:2,5 searched ^[1] 129:20 searches ^[2] 20:9 269:7 seats ^[3] 184:13 185:2,13 SEBILLE ^[2] 322:3,3 Second ^[29] 70:16 84:19 85:14 96:8,13,14,20 128:20 135:17 159:3 180:2 185:14 198:5 250:17 254:2,10 260:11 277:11 284:16,18 286:9 303:22 317:1,5 328:4 336:4 340:12 348:8 375:3 secondary ^[1] 322:11 secondhand ^[1] 117:12 Secondly ^[1] 115:20 Secretary ^[1] 2:3 Secretary/Treasurer ^[1] 4:11 secreted ^[2] 64:14,18 secretion ^[1] 64:21 section ^[5] 51:22 182:10,12 183:2 184:6 sections ^[1] 218:5 sedative ^[1] 227:1 sedatives ^[1] 227:12 see ^[124] 16:18 20:10 22:12 23:4 27:8 30:9 32:5 34:1,1 38:8 39:19 41:5 43:16 47:19 53:9 54:6 55:10 56:2,16,17, 22 57:6 58:6,12,13,14 62:22 63:16 64:17 75:15 81:11 83:14 95:20 99:11 100:14 103:21 106:12 108:8,9,10 112:22 131:18 132:16,19 143:13 144:18 145:8,17 159:3,22 160:7,16 166:18 167:18 168:7 169:17,20 171:13 175:12 177:13 178:8 179:19 192:14 197:13 202:3,8,15 205:15 206:7 209:19 212:20 216:1 217:4,16,18 218:9 228:3 235:3,4 236:21 248:12 256:6,19 262:12,18 263:13 264:5,17 265:11,12,17 271:18 272:2 279:5,15 281:3 285:17 286:6 291:19 292:17 294:11,22 295:16 301:7 305:10 311:5 313:17 315:11 316:5 322:12 332:19 341:2 345:18 353:2, 21 356:20 358:13 360:9 366:8,16 372:12 375:3 376:7 378:12 seeing ^[4] 249:3 263:21 298:5 314:10 seek ^[1] 314:5 seem ^[10] 171:4 241:2 315:16 351:9,10,10 358:17 362:8 368:18 378:6 seemed ^[2] 315:7 364:4 seems ^[12] 228:17 237:22 239:1,20 278:1 317:16 330:13 331:1 340:19 345:16 356:8 358:19</p>	<p>seen ^[37] 19:5 42:2 52:21 57:13 59:3 78:6 87:7,19 107:18 119:20 142:5 159:5 167:4 169:5 184:1 194:21 199:19 200:3 206:7 208:11 209:8,9 212:12,19 226:16,19 235:1 255:9 267:12 268:11,17 319:19 322:6 323:19 328:9 354:10 377:15 seize ^[1] 216:15 seizure ^[47] 130:15 137:2,2 143:3 207:7 208:19 210:4,9, 19 211:5 215:22 217:18 258:14 269:4,8,12,14,18 270:9,22 271:3,9,11,22 272:3,10,18,21 273:1 297:18 319:1,10,18 320:6,21,22 341:5,5,13,14,16, 21 351:12 366:13 376:1,3,4 seizures ^[49] 12:15 47:19 66:14 95:11 101:11 129:6,9,13, 15,22 130:1,5,13 131:4,7,8 133:11,17 134:7,12 136:18 200:4 202:4 206:4 209:17 210:19 211:11,12,14 214:5 216:4 239:8 251:21 260:2 269:5 270:1 318:19 319:3,4, 7 320:10,12,16,18 329:6 341:18 375:4,8 376:8 select ^[1] 298:5 selection ^[1] 284:3 selective ^[5] 42:3 51:16 196:14,15 251:13 selectively ^[1] 192:7 selectivity ^[1] 52:21 self ^[1] 70:14 self-assessed ^[1] 102:2 self-assessment ^[1] 153:16 self-esteem ^[1] 91:7 self-injurious ^[3] 22:12 23:19,22 self-mutilating ^[1] 22:17 semi-starvation ^[1] 291:4 sends ^[1] 238:20 Senior ^[1] 7:4 sensations ^[2] 52:6 191:13 sense ^[8] 35:4 164:16 219:21 261:16 294:9 301:15 305:7 314:11 sensitive ^[3] 215:19 216:2,3 sensitivity ^[10] 22:20 65:6 101:22 200:6 260:10 284:14 286:8 316:20 317:1 324:1 sensory ^[10] 67:8 124:1,8 194:10 201:15 202:5 260:15 262:3,9,9 sent ^[6] 21:3 295:2 308:13 315:17 338:8,10 separate ^[4] 21:21 238:15 300:20 328:20 September ^[2] 144:18 308:21 sequence ^[1] 203:22 SERENADE ^[15] 39:15 44:14 46:9 85:20 86:4,11,16 88:1, 16 95:17 99:22 265:7,8,14 266:5 series ^[6] 11:14 138:11 156:3</p>	<p>301:1,8 308:20 serious ^[25] 20:22 31:20 108:14 118:1 125:2 136:14 157:17 180:16 205:6 238:12 244:11 346:1 347:20 348:1 349:20 350:6,9,18 352:11,13 371:11,20 375:19,20 376:1 seriousness ^[2] 17:1 181:6 serotonin ^[3] 59:15 183:11 194:17 serve ^[3] 10:17 193:18 230:9 SERVICES ^[2] 1:1 7:13 session ^[5] 11:17 185:14 221:4 222:19 327:2 set ^[12] 19:17 22:7 64:7 71:7 148:4 170:22 171:14 173:8 260:19 307:12 311:22 347:15 sets ^[1] 327:10 setting ^[4] 31:1,5,10 298:7 settings ^[2] 16:15 27:12 settles ^[1] 339:22 seven ^[1] 266:9 several ^[11] 72:10 115:9 147:2 161:1 164:4 194:6 282:16 302:11 312:7 333:6 368:5 severe ^[10] 18:18,20 102:14 144:20,21 145:4,10 274:16 280:3 290:21 severity ^[7] 18:17 23:6 29:5 31:11 313:9 347:5 378:16 sexual ^[2] 91:7 288:17 SF-36 ^[4] 90:21 178:1,19 179:15 shaking ^[1] 375:12 shame ^[1] 238:7 share ^[1] 90:19 she ^[11] 6:5 9:15 14:21 103:4 109:14 243:7 266:10 316:3 333:13,15 374:18 shift ^[2] 196:21 378:4 shoot ^[1] 352:20 short-term ^[4] 73:13 125:9 140:13 322:7 shorter ^[1] 86:16 Shortly ^[2] 144:12 191:10 should ^[45] 12:5,21 13:3 17:6 18:19,20 20:19 24:9 112:3 126:4 147:5 148:17 154:16 156:20 157:6 160:12,13 166:4 167:17 181:14 231:17 238:10 239:18,21 242:6 252:16 255:19 258:7 264:20 267:14 270:12 274:20 277:13 285:6 286:5,8 300:2 323:7 359:9 365:10,11 374:18 378:20 381:8 383:16 shouldn't ^[1] 25:17 show ^[17] 28:15,16 64:19 80:19 112:6 143:18 144:6 149:5 182:20 213:21 214:20 218:22 222:13 247:14 248:3 294:5 338:13 showed ^[12] 66:16 106:6 114:2 133:3 171:1 205:4 249:19 255:10 307:15 333:6 345:22 354:20</p>	<p>showing ^[8] 44:6,22 170:17 182:18 225:18 228:6 247:9 249:21 shown ^[68] 28:18 51:21 52:22 53:12 54:2,21 56:12 58:1 59:13 61:15 62:12,17 63:1,6 64:9,13 65:19,20 66:4 70:6 71:7 72:17 75:2,5,6,17 77:4 78:22 79:4,20 82:17 83:4,22 85:22 86:19 87:4,5 88:17 89:21 90:2,11 95:15 98:14 99:5,8 101:4 103:10 109:20 111:3,20 112:13 113:7 124:7 125:7 134:12,21 136:5 137:3 198:17,21 205:13 207:11 210:22 227:19 230:16 233:19 252:22 350:15 shows ^[20] 16:17 56:2,9 61:18 74:19 78:9 116:14,18 126:10 170:19 201:16,19 205:11 207:22 208:18 209:16 294:15 295:11 315:9 334:21 sibutramine ^[25] 73:21 137:11,18,21 138:1 162:2 182:8, 14,16,21 183:2,7,14 229:8 255:9 294:17 295:5,7,15,20, 21 296:16 315:1 328:11 330:15 Sid ^[5] 2:13 6:22 223:19 241:13 374:15 side ^[28] 6:1 21:13 27:17 34:3 104:20 105:19 106:16,18,20, 21 149:6,18 154:16 161:10 162:1 165:13 166:19 169:22 230:1 245:5 289:11,12 333:20 347:3 351:8 356:13 362:18 375:15 side-effect ^[1] 366:8 sides ^[1] 133:8 sidewalk ^[1] 274:2 Sidney ^[4] 4:3 223:18,22 224:1 sign ^[1] 119:4 signal ^[13] 28:15,16 113:3 136:17,17 184:1 195:17 219:1 269:3 291:18 314:21 354:11 357:16 signaling ^[6] 60:8 186:15 188:13 192:7 193:19,20 signals ^[4] 134:22 205:4 257:12 298:4 significance ^[9] 65:2 121:3 229:20 252:2 263:6 264:19 278:8 286:1 297:17 significant ^[33] 19:12 67:8 72:7,12 80:22 87:9 88:10 92:4,5 111:21 113:16 123:16 179:12 205:5 210:14 214:5 226:13,17,18 227:14 229:4 232:19 236:16 255:10,16,20 270:14 274:15 275:12 291:5 354:11 356:15 366:9 significantly ^[23] 19:12 31:8 75:12 82:4 87:22 88:17 91:9 92:8,15 116:8,15 177:16 179:4 195:13 226:22 227:11,19 233:9 234:5 244:7 252:9,14</p>
---	---	---	--

<p>367:5 signs ^[3] 119:5 202:15 268:12 Silver ^[2] 1:9,11 similar ^[39] 26:9 34:12 75:15 80:10 86:8 99:11 100:8 103:13 104:1,8,14 105:1,2,19 106:6 115:3 116:1 119:16 121:22 125:17 129:1 130:21 133:20, 20 135:16 183:10 197:19 204:3 209:9 213:8,21 214:17 245:12 246:11 292:13 307:19 360:20 367:12 374:21 similarity ^[3] 202:21,22 331:4 Similarly ^[7] 60:7 104:13 124:8 209:6 210:16 248:6 255:15 simple ^[3] 54:12 149:19,21 simplified ^[2] 132:12 149:20 simply ^[3] 220:12 281:17 348:17 simultaneously ^[1] 43:22 since ^[15] 14:4,6 28:17 47:8 73:12 86:15 89:6 90:11 135:2 294:21 296:14,17 314:13, 14 328:19 single ^[3] 90:1 166:12 257:10 site ^[13] 18:6 102:12,17 103:20 104:12 151:13 197:6,19 224:11,17 287:7 306:5,8 sites ^[5] 102:10 108:22 130:10 224:12 226:6 situation ^[5] 56:5 61:2 105:21 335:10 383:8 situations ^[2] 26:1 88:1 six ^[1] 204:15 six-fold ^[1] 227:13 Size ^[7] 4:8 38:7,8 46:6 231:6 235:10 265:12 sizes ^[3] 256:12 259:9 315:13 skeletal ^[4] 52:11 67:11 189:15 201:1 sketchy ^[2] 287:11 341:10 skilled ^[1] 313:4 skin ^[1] 167:2 Skip ^[1] 106:15 slap ^[3] 18:10,12 30:2 sleep ^[11] 70:18 72:11 159:4 161:7 200:5 202:16 244:10 276:17 277:19 282:4 293:17 sleeping ^[1] 154:21 slept ^[1] 119:8 slice ^[1] 58:18 Slide ^[333] 15:9,13,22 16:7 17:2,10 18:8 19:14 20:5 21:5,18 23:2,9 24:14 25:3 26:12,21 28:5 29:1,11,14 30:8,14,16, 20 31:12 32:1,8,22 35:7 37:11 38:1,11,20 39:17,20 40:12 41:1,22 42:10 43:8 44:9 45:2 46:14,20 48:6,16,19 49:1,13, 19 50:8 51:18 52:15 53:17 54:1 55:16,22 58:1 59:5 61:4, 18 62:8 63:4 64:6 65:10 66:22 67:20 68:21 69:10,17 70:1,9 71:2,22 72:15 74:2,13,18 75:7,16,21 76:5 77:3,6,12 78:7,8 79:19,21 80:7 81:10 82:9,</p>	<p>19 83:13 84:5,13 85:7,12 86:13 87:21 88:13,22 89:9 90:7, 18 91:4,12 92:2 93:16 94:6, 20 95:12 97:9,13 98:2,13 99:9 100:5,11,20 101:1,12 103:7, 17 105:11,13,21 107:6 108:12,20 109:18 111:2 112:13, 14 113:22 116:17 117:15 118:20 119:13 121:11 122:17 123:6,21 125:18 126:7 127:17 128:6,11 129:4 130:12 131:10 132:10,21 133:9 134:13 137:7 139:4 140:6,14, 20 141:2,3 142:13,16 143:10 146:12 147:8 148:11,20 149:16 151:4,18 152:16 153:9,22 154:6 155:15 156:1,15 157:1, 11 159:16 160:15 163:18 164:17 165:9 166:17 167:12 168:6 169:2 170:17 175:11 177:6,22 182:5 186:1,13 187:17,22 188:19 190:9,10,21 191:20 192:14 193:2 194:3, 22 196:11 197:1,21 199:6 201:3,12,13 202:17 203:14 204:5,6 205:10,11 207:5,21, 22 208:17,18 209:15,16 210:2,5 211:1,3,4,18 212:16,17 213:9 214:9 247:7,8,9 248:16,17 249:19,21 251:11,15 252:3,18 253:11,17 254:9 255:4 256:3,4,16,17 257:7 259:3,14 260:12,22 261:9 262:5,6 263:1,2,22 264:1,11, 12,20 265:5 267:1,11 269:2,9, 19 270:11,20 271:20,21 272:8,15 273:4,12 274:4 275:9,15 276:1,2,22 278:2,9,20 279:9 280:13 281:19 282:11 283:3, 4,10 284:5,19 285:10,11 286:2,12 287:13 288:10 289:8,20 291:1,8,10 292:1,5,18 293:9 294:1 296:9,21 299:2,16,20 311:4,5 313:13,13 315:9 326:3 350:14 Slide.]f ^[1] 73:16 slides ^[15] 53:20 56:17 67:1 95:19 106:7 108:16 157:3 175:21 222:13 246:21 247:4 250:16 251:3 261:22 358:19 slightly ^[4] 205:19 265:3 275:17 278:22 slippage ^[1] 163:6 slowing ^[1] 267:9 slowly ^[1] 60:16 small ^[12] 104:18,19 244:20 265:18 267:14 272:12 285:17 298:5 324:6 325:2 332:21 364:19 smaller ^[2] 310:15,15 smart ^[1] 237:13 smell ^[1] 262:20 smoke ^[1] 363:18 smokers ^[4] 256:8 311:7 321:12 322:14 smoking ^[23] 40:9 94:13 97:10 109:3 110:10 111:17 114:</p>	<p>17,21 315:8,10 316:19 321:15,21 322:6,8,20 324:2,6,19 338:20 346:18 363:19,21 smoking-cessation ^[8] 267:22 284:8 285:8,13 286:5 344:22 345:1,15 SMPC ^[1] 44:3 so ^[287] 5:7,21 6:5 10:14 17:3, 17 19:2,4,8,15,21 20:9 21:2, 8,17 22:1,8,19 24:1,8 25:4, 10 26:8,22 28:1,8,14 30:2,6, 12 31:2,21 35:16,22 36:2 40:15 47:11 48:1 54:22 55:6 58:9 59:6,16 61:5 62:9 63:5 64:19 65:2,11 66:4 68:17 94:8 96:10,11 97:6 100:6 104:11 105:1,8 106:14,22 107:4,7 108:18 109:22 110:18,20 116:2 117:7 120:13 124:20 125:15 126:22 130:4,5 132:22 133:7 138:9 142:20 143:5, 20 145:20 146:13 148:1,13 149:14 150:13 151:1 152:4, 17 153:2,13 154:19 156:10, 16,22 157:5 160:6 165:4 167:21 168:7 170:10,21 171:3,8 172:4,7 173:3,8,9,15 175:6 176:14 179:17,20 181:9,13 182:20 184:7,20 197:22 199:1 201:20 203:15 208:15 213:10 217:5 218:22 219:18 220:5,7,19 222:12 223:17 225:5, 17 232:21 236:13,16,16,17 237:5,19 238:4,6,18 239:5,17, 22 240:21 241:8 242:2,5,14 247:16,22 249:2,5,20 251:22 258:7 265:6,17 270:7 271:14 286:4 291:21 292:15,19 294:7,14,19 295:4,9,16 296:6 301:7,21 302:11,16,21 304:4,9,14 306:2,12,14,20 307:9,10 308:17 309:12 310:8 311:22 312:15 313:2,7,20 314:2 315:2,14 316:7 321:5 322:14 323:6,19 324:7,21 325:2,3,19 328:2,13 329:17 332:15 333:1,4 335:3, 17 336:22 339:22 341:15,20 342:11,13,18 343:16 344:7, 14 346:10,16 347:6,16 348:10 349:22 351:7,14,15,17 352:4 353:9,18,19,22 354:5, 14,17 355:2,19,21 358:7,14, 21 359:17,18 360:16 361:16, 22 363:8,20 364:7,8 365:15, 17 367:13,16 370:6,11,22 371:19 372:1,11 373:3,5 375:5,13,14,16 376:2 377:7 379:5, 9 380:10 381:15 382:12 384:21 385:1 so-called ^[2] 114:5 291:4 SOC ^[1] 276:9 social ^[8] 70:13,14 178:5 235:16 236:6,15 245:15 288:3 societies ^[1] 146:4 Society ^[8] 4:12 158:9 243:8, 12,13,16,22 351:13 sodium ^[1] 195:3</p>	<p>softer ^[1] 356:16 solely ^[1] 65:4 some ^[116] 12:3 13:20 15:10 21:12 22:9 23:19 28:7 33:1 42:12 44:6,22 53:7,19 59:8, 16 61:7 65:7 72:3 91:22 112:1 130:9 134:15 140:15 142:5 143:19 144:16 155:21 157:9 164:1 166:21 175:2 182:6,18 184:5 191:21 211:4,21 216:3 218:17 220:7 222:11 226:1 227:4 233:7 234:2,6 235:15, 17,17,18 237:2,10 239:4 242:2 245:5 246:21 247:4 254:7 259:1 278:10 281:13 293:21 294:3 303:3,7 306:2 312:15, 17,19 315:8 316:5 331:18 333:1,9 334:2,21 339:15 341:9,14 343:9,11 344:22 345:4 350:16 351:4,9 354:9 355:10 356:14,15,18,18,21 357:17, 18 358:20 359:20,22 360:2,3, 18 362:8 365:5 367:13 368:20 369:13,18,19,20 370:2 373:18 375:3 376:1 380:20 381:6 385:6 Somebody ^[6] 18:12 31:3 170:10 351:11,11 368:14 someone ^[2] 324:1 338:6 something ^[29] 5:12 21:14 27:14 35:4 135:7 141:18 143:16 152:11 153:19 174:11 218:9 237:12 239:14 240:17 241:18 242:9 314:18 316:4 326:20 330:3 331:8,10 346:15 355:16 374:21 376:19 377:17,18 382:19 sometimes ^[4] 60:14 103:19 110:16 153:2 somewhat ^[10] 28:20 81:6 99:15 104:20 194:13 350:12 364:5,6 365:21 372:20 somewhere ^[2] 18:12 344:13 somnolence ^[2] 202:13 276:19 soon ^[3] 142:21 167:15 294:6 sore ^[1] 302:19 sorry ^[8] 274:20 308:4 311:16 323:2 334:22 337:18 343:1 384:21 sort ^[19] 35:20 51:11 58:19 174:14 306:2 315:22 326:17 330:14,18 333:14 334:21 341:10 349:6 354:15 355:18 360:14 362:12 378:4 381:9 sorts ^[2] 297:4 303:13 sought ^[1] 48:2 source ^[4] 102:20 108:22 110:15 130:9 Spanish ^[1] 152:5 spasms ^[3] 99:12 100:10 267:4 spasticity ^[1] 267:4 speak ^[4] 5:16 19:18 359:17 360:19 Speaker ^[8] 3:9 9:12 13:14 14:20 15:3 223:2 235:8 243:</p>
---	--	--	--

<p>7 speaking [4] 8:10 223:16 343:21 356:5 special [6] 94:3 101:10 114:11,13 135:6 334:19 specialist [1] 118:4 species [18] 54:16 186:9,12 202:19 204:1,4,12 205:13 206:20 208:2,5 211:5,12 212:13 213:8,12 214:20 247:10 specific [30] 34:9 51:3,3 92:14 101:14 102:17 143:2 144:17 193:3 216:7,7 217:22 219:8 220:6 230:17 237:11 239:5 251:19 258:12 260:19 305:7 314:16 319:10,19 368:17,20 371:17 374:16,20 375:21 specifically [23] 11:3 41:6 93:18 98:9 101:16 144:7 182:2 194:12 195:7 212:7 218:8 251:20 288:6 292:9,21 297:12,15 305:10 332:8,17 366:7 368:4 369:13 specificity [3] 301:7 369:17 381:14 specified [3] 262:7 263:3,7 specify [1] 160:11 spectacular [1] 300:6 spectrum [3] 162:7 188:14 206:6 speculated [1] 269:13 spend [6] 27:1 33:21 236:19 258:11 347:19 377:4 spent [1] 71:15 spinal [1] 218:6 spine [2] 189:13 191:12 spinning [2] 301:15 302:3 spite [2] 106:8 241:22 split [1] 133:16 spoke [1] 111:8 spoken [1] 326:12 SPONSOR [60] 3:11 9:16 13:10 26:16 36:12,15 96:3 108:21 112:7 115:17 116:10 127:4,15 130:13 131:2,11 133:1 138:11 139:12 157:12 170:11 182:4 204:10 210:5 217:15 219:8,12 223:5 287:2 292:11 301:6,8 302:6,7 303:2,8 304:13,17 310:1 316:8,11 320:1,2,9 325:8 327:6 329:20 336:15 345:5 347:13,15 352:19 358:19 368:3 372:1,22 373:10 374:13 380:17 385:11 sponsor's [9] 223:8 258:18 259:1 263:7 308:8 317:17 318:21 348:12 354:14 sponsors [4] 252:17 334:20 370:5 373:7 spontaneous [4] 28:16 102:1 233:10 327:18 spontaneously [3] 143:4 295:2 296:11 spot [1] 149:15 spread [1] 257:11 spreads [1] 353:3</p>	<p>Spring [2] 1:9,11 SR141716 [1] 56:18 SSRI [1] 118:15 stab [1] 19:9 stability [1] 62:16 Staff [3] 7:3 324:15 370:4 stage [1] 219:14 stakeholders [2] 146:3,8 stand-in [1] 111:15 standard [8] 200:16 204:9,19,21 210:21 276:4 291:15 305:4 standardized [2] 16:17 109:16 standards [2] 245:11 246:10 standing [1] 10:18 stands [1] 39:1 Stanley [1] 16:2 start [21] 5:9,20 6:1,5 14:19 36:10,12 74:15 118:12 142:17,20,21 146:10 170:13 215:17 328:22 329:12 340:5 376:9 382:2 383:12 start-up [1] 34:15 started [7] 73:8 85:10 174:17 185:13 234:10 247:6 275:4 starting [8] 8:11 66:8 127:13,21 128:2 167:6 268:7 336:5 startle [1] 202:9 State [15] 9:13 14:22 55:1,15 57:3 73:6,12 196:22 198:10,10 264:9 306:1 307:8 334:22 380:21 stated [1] 252:6 Statement [11] 3:5 8:13,14 223:3,11,15 230:20 234:16,17 334:15 335:12 statements [2] 123:3 244:1 States [8] 44:17,18 45:3 69:19 143:18 146:5 157:17 234:11 static [1] 145:18 statin [2] 78:20 348:4 statistical [13] 48:22 89:13 254:19 255:10 259:4,15 262:8 263:4 264:18 278:8 286:1 331:21 360:7 statistically [7] 111:21 178:9 179:4,12 210:13 226:13 227:14 statistician [2] 7:19 324:13 statisticians [1] 284:3 statistics [2] 35:7 331:1 status [1] 43:10 stay [5] 33:16 77:10 84:18 170:10 380:3 stayed [2] 84:21 241:21 steady [1] 57:3 steep [1] 160:6 step [2] 68:17 75:8 stepping [1] 352:5 Steve [4] 8:6,8 369:9 370:10 Steven [3] 2:20 9:1 14:5 stick [2] 5:8 377:20 sticks [1] 333:15 stigma [1] 245:15 still [24] 24:3 58:18 66:2,12</p>	<p>73:20 81:7 82:16 85:17 139:3 172:7 182:19 233:16 281:16 286:7 298:3 353:18 354:9,16,21 358:4 360:5 374:2,6 376:9 stimulate [1] 56:19 stimulated [3] 54:6 192:9 327:21 stimulates [1] 64:20 stimulation [3] 164:7 189:22 195:20 stimuli [1] 51:4 stimulus [3] 199:11 202:14 214:16 stomachache [1] 27:17 stop [7] 40:13 41:3 104:4 237:21 321:15,21 379:1 stopped [5] 41:2 85:9,10 287:4,6 storage [2] 67:13 68:2 stored [2] 51:1 188:7 story [4] 17:12,13 165:7 371:12 straddles [3] 132:7,20 133:6 straddling [1] 131:22 STRADIVARIUS [2] 117:18 286:21 strains [3] 216:2,3,7 strand [1] 233:12 strange [1] 239:4 strata [2] 87:18,20 strategies [1] 168:22 strategy [3] 159:11 167:16 170:1 stratified [3] 87:13 259:7,20 STRATUS [3] 109:2 114:18 116:2 STRATUS-worldwide [2] 111:16 115:22 strengths [1] 255:2 stress [5] 186:21 191:1 225:13 276:14 336:14 stressing [3] 148:6 150:18 151:15 stressors [2] 113:16 118:2 strict [1] 191:18 stricture [1] 166:9 string [3] 20:9 130:2 269:6 stringent [1] 356:9 stroke [1] 299:11 strongly [5] 64:2 229:11 234:16 292:7 331:13 struck [1] 341:7 structure [4] 62:12 111:11 115:7 187:21 studied [16] 38:14 42:14 63:21 65:14 85:16 86:17 87:16,18 88:1 186:22 189:20 228:1,8 323:5 339:21 343:5 studies [216] 21:20 22:7 27:5,6,7 29:16 31:18 32:16 37:4 38:9,21 39:6,7,11 40:3,18 41:12,21 44:14 45:15 57:4 59:1 61:1 62:11 63:5 65:11 67:2 76:1,3,4,14,15,16 77:15,22 79:1,10,20 80:10 81:12 82:5 83:16,17,19,21 85:22 86:8</p>	<p>87:14,17 94:1 95:14,21,22 96:17,19 97:15,16,21 98:15 101:8,16 102:4 103:2 107:18,21 109:5,6,7,9,10 110:7,9,13 111:9,12,14 112:16,16 113:1,7 114:12 115:18 116:1,12 119:14,15,16 120:19 121:14,17,21,22 124:7,8 129:20 130:15,21 131:3 132:9 133:2,10,21 134:4 136:20,21,22 164:4 165:19 171:1 175:12 180:20 186:7 198:17,20 204:7,10,11,12,14,18,20,21 205:1 206:14,18 207:1 209:1,3,3,7,10,11 210:3 214:20 215:3 216:7,22 217:6,9,13 218:5,18 226:19 228:4 229:5,15,18 230:7,14,15,19 232:7,22 233:17,19 234:13 241:15 253:22 254:11 256:15,15 257:16 258:19 259:7,10,17 260:21 265:6,10,20 267:5,18,20 269:8 272:2,3,9 274:13 275:6,12 277:4 278:5 281:6 284:3,6,17 285:22 286:4 287:19 290:3 292:4 298:16 300:6,14 308:20 310:18 311:20 312:4 317:4 322:8,10 325:6 336:13 347:22 348:4 360:3,8 364:16 365:7 367:7 368:9,22 369:2 377:8 381:5 382:15 study [111] 21:8 30:9 31:5,13 32:15 38:7 39:14 41:8 66:14 72:18 74:19 75:9 76:21 79:13 81:15 83:3 84:15,16 87:14 88:16 95:17 99:20,22 103:4 106:2 111:16,19 114:18,19,20 115:6,22 116:11 117:18 118:12 120:11 128:22 129:2,2 130:18 134:5 171:16 173:11,12 178:9 181:1 210:6 218:8,21 225:16 228:20 241:19,19 254:18 255:6 257:21 259:7,21,22 265:8 266:12,15 275:4,15 277:5 280:16,18,21 284:12 286:22 289:13 293:7 299:6,10,12 300:12,20 312:14 313:19 315:8 316:18,19,22 322:9 324:18,19 325:6 331:14 332:7,12,13 334:16 344:22 345:1,15 348:22 349:22 364:20 365:5 366:19 367:2,9 368:19 371:1 373:2,3 377:1,22 378:21 379:12 380:15 stuff [2] 237:6 333:9 subacute [2] 209:2,10 subclassifications [1] 103:13 subcutaneous [1] 61:20 subgroup [7] 91:2 354:15,22 355:3,18 356:11 374:19 subject [10] 79:13 175:16 176:3 266:8,17 267:19 268:3 282:13 327:20 374:17 subjects [61] 61:21 62:2 252:12,15 253:3,6,10 254:3 255:13,19 256:9,22 257:17,19</p>
--	--	---	--

<p>261:13,14,20,21 262:15 263:9,9,15 265:7 267:17,21 268:20 270:12,17 274:13 275:11 277:1,4,6,10 279:11,21 280:2,6,18,19,19,21 281:4,10,13 282:6 286:17 288:2 289:9 290:2,6,10,11,18 291:4,11,13 292:21 309:5 318:17 350:20</p> <p>subjects^[1] 265:2</p> <p>submission^[3] 46:15 270:21 282:12</p> <p>submit^[1] 46:9</p> <p>submitted^[8] 43:13 45:4,5,13 135:10 139:10 205:7 283:12</p> <p>subpopulation^[2] 265:16 355:4</p> <p>subpopulations^[2] 51:22 191:17</p> <p>subscore^[1] 102:6</p> <p>subsequent^[5] 97:7 109:21 188:11 207:17 269:17</p> <p>Subsequently^[2] 15:17 282:20</p> <p>subset^[1] 377:2</p> <p>subsets^[1] 179:18</p> <p>substantially^[1] 116:9</p> <p>substitute^[1] 307:5</p> <p>suburban^[1] 6:18</p> <p>succeeding^[1] 237:5</p> <p>succinct^[1] 367:19</p> <p>such^[46] 8:18 18:14 51:14 52:14 56:7 59:20 60:16 70:18,22 73:5 95:10 100:9 124:1 126:6 129:11,15 180:12 183:3 191:9 193:15,17 195:7 197:10 210:6 222:18 223:12 225:15 257:18 260:2,5 268:13 273:14 276:13 279:19 289:11,16 291:6 298:16 300:15 304:5 317:19 332:13 335:2 343:13 345:3 368:7</p> <p>suffer^[2] 381:14 382:11</p> <p>suffering^[2] 70:17,20</p> <p>sufficiency^[1] 135:11</p> <p>sufficient^[9] 116:21 199:7 203:9 214:13 244:21 342:14 349:12,13 351:18</p> <p>sufficiently^[2] 12:19 335:19</p> <p>suggest^[2] 267:6 335:14</p> <p>suggested^[6] 134:2 152:7 205:1 268:5 287:19 288:15</p> <p>suggesting^[5] 61:13 62:5 63:11 68:10 377:7</p> <p>suggestion^[3] 308:14 372:14 373:18</p> <p>suggests^[7] 51:9 191:8 207:15 212:5 229:11 360:8 363:3</p> <p>suicidal^[73] 14:21 15:5 16:12 17:7,9 20:20 21:21 22:4,5,10 23:1 24:11,15 25:10 27:19 29:4 30:2,4 32:12 33:1,3,10 35:9,20 108:17 110:1,5 111:5,6 112:12,21,22 113:2,6 119:6,18,21 120:10,20 121:15,18 122:2,6,11 135:18 137:16,20 266:7 282:13 283:7,8,</p>	<p>15,18,19 285:1,4,9 288:2,21 289:4 291:3,7 292:21 293:17 296:12,15,17,20 297:15 310:9 314:21 340:13 361:4</p> <p>suicidality^[72] 11:12 12:14 15:4,12,20 16:8 17:22 22:8 23:5,8 24:8 27:6 32:11 46:1 47:15 95:11 98:10 101:6 102:8 108:3,16 109:22 110:14 115:21 116:15 120:18 121:4 122:15 136:9 139:16 147:14 153:6 168:22 183:18,22 184:3 226:14 227:7,16 251:22 258:15 260:2 282:19,22 284:4,16,20 285:2,21 287:9,15,21 290:1,7 291:11,13,18 292:14,20 293:4 297:15 300:12 308:11 310:4,13 312:19 315:7 329:5 354:13 366:10 378:3</p> <p>suicidality-related^[1] 121:12</p> <p>suicide^[48] 11:9,12 18:13 19:11 20:2,10 22:5,5 23:13,14,18 24:4 25:13,15,16,18 28:11,12 29:5 30:3 31:9 33:11 102:19 108:15 112:17,19 116:22 117:1,2,10,11 118:15 119:2 120:6,8,15,16 121:19 122:4 137:17 200:14 274:19 284:22 285:4,6 286:16 287:5 350:11</p> <p>suicides^[8] 120:9 122:4 136:1 183:15,16 286:13 300:10 352:16</p> <p>suitable^[1] 335:4</p> <p>sulfonylurea^[8] 39:14 46:19 76:13 85:19 86:18 87:7 91:21 99:19</p> <p>sum^[3] 67:1 74:3 92:3</p> <p>summarize^[9] 42:11 67:21 94:8 203:15 213:10 251:16 269:22 286:19 349:18</p> <p>summarized^[1] 109:3</p> <p>summarizes^[6] 201:13 204:6 210:5 211:4 212:17 262:6</p> <p>summary^[8] 11:8 107:7 132:22 156:16 205:11 256:17 264:12 292:19</p> <p>summer^[1] 224:6</p> <p>Supervisory^[1] 6:15</p> <p>supplement^[1] 134:8</p> <p>supplemental^[1] 114:2</p> <p>supplements^[2] 71:17 161:14</p> <p>supply^[1] 240:9</p> <p>support^[11] 9:16 15:17,21 23:15 28:6 48:22 64:2 92:19 204:7 291:22 328:1</p> <p>supported^[2] 205:8 243:19</p> <p>supporting^[3] 74:16 85:14 214:7</p> <p>supportive^[1] 243:16</p> <p>supports^[1] 193:20</p> <p>supposed^[2] 20:13 361:19</p> <p>sure^[20] 20:20 25:9 149:7 151:9 155:17 178:1 216:15 238:18 239:3,16 240:20 249:</p>	<p>6 300:19 304:15 308:4 310:21 349:11 359:5,6 380:5</p> <p>surgery^[10] 71:19 72:1 73:11 74:6 162:8,10,16 237:18 241:19 245:3</p> <p>surgical^[1] 162:18</p> <p>surprised^[1] 334:21</p> <p>surprising^[7] 81:5 226:15 292:16,17 293:18 295:20 331:4</p> <p>Surprisingly^[1] 52:7</p> <p>surrogate^[3] 165:1 298:18 299:15</p> <p>surveillance^[4] 32:6 40:17 143:4 241:5</p> <p>survey^[6] 143:12,16 144:8,13 149:2 376:20</p> <p>surveys^[3] 152:15,15 156:3</p> <p>survival^[2] 66:21 68:13</p> <p>survivors^[1] 365:11</p> <p>susceptible^[4] 159:12 167:13 169:22 290:22</p> <p>suspect^[1] 235:2</p> <p>suspected^[4] 127:16 148:16 268:1 271:9</p> <p>suspicion^[1] 334:2</p> <p>sustained^[1] 63:11</p> <p>sweating^[1] 301:19</p> <p>Swedish^[2] 101:13 241:18</p> <p>swiftly^[1] 144:22</p> <p>switch^[1] 77:11</p> <p>switched^[2] 84:19 85:1</p> <p>symptom^[9] 33:4,5 101:18 277:7 290:7 292:15 301:10,11 306:4</p> <p>symptomatic^[1] 100:2</p> <p>symptoms^[41] 17:18 102:18 105:9 119:3 123:8 124:1 126:5 167:14 260:15,20 264:7 266:9,11 268:12 273:5,8 274:1,6 275:21 276:12 279:2 280:22 281:15 282:3 288:21 289:4 307:11 310:9,13 312:18,19 313:5 341:3 361:5 362:13 368:6 369:2 373:21 374:8,22 378:2</p> <p>synapses^[1] 193:16</p> <p>synapsis^[2] 193:15,17</p> <p>synaptic^[4] 192:4,8 193:22 207:14</p> <p>syncope^[1] 305:21</p> <p>syndrome^[1] 312:11</p> <p>synthesis^[4] 57:18 188:16 192:3 269:15</p> <p>synthesize^[1] 192:22</p> <p>synthesized^[2] 50:22 188:6</p> <p>synthesizing^[1] 51:6</p> <p>synthetic^[2] 58:7,15</p> <p>system^[125] 19:3 20:3 23:11 26:6,14 29:6 49:21 50:3,10 51:8,10 54:5 56:3 58:11,16 59:6 60:10 61:6,9,14 62:6,10 64:22 65:3 67:21,22 68:7 98:18 99:2 133:12 158:21 163:22 185:21 186:4,8,11,14,15,18,20 187:1,7,15,19 188:18 189:6,12 190:3,8,12,15 191:</p>	<p>22 192:10 194:5 195:4,7,15 196:13 198:19 199:10,12,13,16,19 200:15,17,18 201:22 202:6,12,22 203:17,19,20 205:2,4 206:8,15 207:9 211:10,21 212:10,12,18 213:2,7,11,14,17,20 214:8,19 215:9 225:6,10,12,12,19 226:4 231:20 232:11 233:20 237:7 242:13 269:11 276:8 283:6 292:9,10 295:1,3,10,19 296:3 298:3 302:14 312:21,22 365:22 366:6 370:14,20 371:15 381:8,18</p> <p>system's^[1] 207:16</p> <p>system-mediated^[1] 214:16</p> <p>systematic^[10] 16:16 28:1,8,12 29:3 30:6 32:10 254:3 268:19 372:15</p> <p>systematically^[1] 28:14</p> <p>systematization^[1] 18:22</p> <p>systemic^[1] 211:16</p> <p>systems^[4] 57:12 163:20 226:14 261:8</p> <p>systolic^[1] 253:15</p>
---	---	--	--

T

T^[7] 3:1,1 4:1,1 155:18 201:21 222:1

table^[21] 53:7 77:14 108:7 116:18,20 126:8,9 130:14 132:12,13 208:16 226:16 228:4 248:16 306:9 319:2,21 329:9 338:9,9,13

tables^[2] 341:6 361:3

tablet^[1] 42:8

tablets^[1] 18:4

tabulation^[1] 111:7

tachycardia^[1] 123:18

take^[34] 15:14 131:20 132:2 140:7 154:17 156:8 157:6 171:10 184:13 185:13 208:22 235:12,22 236:20 238:4 239:18,22 243:3 284:1 299:17 300:1,2 302:10 314:20 315:1 325:15 327:4 328:14 334:6 348:2 355:17 361:19 374:11 377:14

take-home^[1] 55:16

taken^[13] 15:21 19:12 137:15 160:22 231:18 237:1 256:21,22 318:22 364:8 369:22 379:10 380:17

taking^[12] 13:14 24:20 179:12 184:3 229:13 236:21 268:3 286:20 288:18 292:21 374:7 379:1

talk^[16] 11:10 49:20,22 146:17,18 154:9 185:5 219:5 222:5 223:18 235:20 237:10 247:2 339:1 350:10 370:11

talked^[4] 155:1 174:12 352:17 372:19

talking^[9] 10:21 16:3 17:14 27:1 33:22 307:22 312:18 325:13 378:7

tamoxifin^[1] 365:12

<p>tandem ^[1] 229:13</p> <p>tangible ^[1] 152:11</p> <p>tapes ^[1] 34:19</p> <p>target ^[9] 11:5 68:16 164:9 190:3 205:2 230:17 336:16 365:7 381:3</p> <p>targeted ^[3] 227:18 245:6 381:9</p> <p>taste ^[2] 174:6 262:19</p> <p>team ^[2] 299:18 324:15</p> <p>teaser ^[1] 304:10</p> <p>technical ^[1] 95:5</p> <p>technique ^[1] 114:4</p> <p>techniques ^[4] 111:10 331:21 334:11,14</p> <p>teleconferences ^[1] 34:17</p> <p>telemeter ^[1] 218:20</p> <p>tell ^[14] 19:6 237:15 238:2,21 304:10,14 314:21 321:22 329:19 333:7 339:19 371:11 373:15 381:20</p> <p>telling ^[3] 237:4 311:12 333:13</p> <p>tells ^[1] 165:7</p> <p>temperature ^[1] 202:8</p> <p>temporarily ^[1] 182:13</p> <p>Temporary ^[2] 2:10 10:18</p> <p>ten ^[1] 293:14</p> <p>tend ^[4] 254:6 308:7 314:4 366:19</p> <p>tended ^[2] 106:22 253:7</p> <p>tension ^[1] 276:14</p> <p>tentative ^[2] 201:2,9</p> <p>teratogenic ^[1] 323:12</p> <p>term ^[12] 17:21 20:12 53:18 64:13 103:9 302:10,12,13,13, 14 306:11 349:3</p> <p>terminal ^[1] 42:20</p> <p>terminated ^[1] 356:22</p> <p>termination ^[1] 269:18</p> <p>terminology ^[2] 16:14 302:9</p> <p>terms ^[52] 20:10,12 23:6 103:14 105:19 139:1 141:8 157:8 176:5,12,22 183:3 225:9 227:5 232:6 236:6 262:7 263:2,5 264:1 276:2,8,10,11,11,13 277:16 278:6 293:14 295:22 304:13,15 305:1,19 306:14 307:2 314:10 345:17 346:14 347:5,5,7 355:21 357:3 358:5,9 360:20 361:15 366:12,20 367:1 379:11</p> <p>terrible ^[1] 301:11</p> <p>terribly ^[1] 261:11</p> <p>terrific ^[1] 380:18</p> <p>Test ^[3] 238:14,15 307:6</p> <p>tested ^[2] 210:22 216:1</p> <p>testifying ^[1] 185:10</p> <p>testimony ^[1] 222:3</p> <p>testing ^[1] 242:18</p> <p>tests ^[1] 239:3</p> <p>text ^[3] 20:9 137:12 286:10</p> <p>TG ^[1] 82:22</p> <p>thalamic ^[1] 225:4</p> <p>than ^[75] 13:6 18:19,20 29:20 38:14 47:4,6 53:15 55:3 56:15 72:3 75:12 78:18 81:6 98:</p>	<p>17 100:16 109:1,10,20 122:20 124:21 134:20 135:1 145:12 160:21 162:17 165:20</p> <p>169:12 171:21 176:12,18,21 189:10 191:8 206:1,21 209:3 212:1 215:19 227:10 229:3 239:1 240:3 248:4 252:9,15 253:2,16 255:13,18 262:10 263:9 264:4 277:3,17 278:22 287:12 289:6 295:6 315:15, 19 320:1 330:17 331:11 332:16 336:18 341:19 344:5 345:16 355:15 357:13 360:8 361:19 376:19 383:18</p> <p>Thank ^[64] 8:8 10:8,13,16,18 13:13 14:13,18 15:7 16:3 33:15 36:9 49:12 68:20,22 92:22 93:1,8 140:1,2 157:18 170:6,9 177:18 184:9 185:19 215:13,14 235:6,7 242:21 243:5,6,10 246:13,15 247:3 250:11 251:1 300:3 303:19 305:14 317:8 320:7 321:6 323:21 325:20 326:22 327:11 335:16,22 342:22 347:16 349:14 351:21 354:2 356:3 362:2 364:11 365:18 369:12 376:10 378:8 383:4</p> <p>thanks ^[4] 14:15 307:13 367:17 370:10</p> <p>that ^[1095] 5:12,15 9:1,10,15, 19 10:4,4 11:14 12:8,17,18 13:2,10 15:15 16:4,6,13 17:3, 5,6,6,8,14 18:15,16 20:1,3,16 21:12,15,17,20 22:10,14,19 23:3,7,17 24:5,11 25:17 26:3, 5,16,19 27:9,12,21,21 28:1,2, 6,17,19,19 29:6,10 30:15 31:1,20 33:3,13,20 34:13 35:1,4, 6,7,12,13 38:8,21 39:18 40:16 41:12,16 42:17 43:19 44:7,8, 12,13,16,17,20 45:1,5 46:6,8 47:19,20 50:22 51:7,9,15 52:5 53:8,9,14,19 54:5,15,17, 21 55:3,4,18 56:9,22 57:6,19 58:13,21 59:10,17,18 60:9 61:8,13,19 62:2,5,13,22 63:6, 11,20,22 64:3,17,19 65:8,20, 21 68:10 69:20,21 70:17 71:6 72:5,19,19 73:1,12 80:16 81:3,5 84:16 85:21 87:9,17 88:16 89:7 90:5 95:3,15 97:6 98:4 99:13,19 102:6,7,7 103:21 105:13,17 106:12 107:11, 20 109:9 110:1,20 111:13,15, 19,22 112:2,7,22 113:5,14 115:4,6 116:2,14 117:2 118:22 119:5 120:6 121:1,7,9,10, 22 122:9 124:5,19,20 125:20 126:4 128:11 130:16 131:8, 18 132:1,2,19 133:8,16,20,20 134:2,8,9,12 135:7,20 137:2 138:5,8,10,14,16 139:2,9,12 140:4,11 141:18 142:1,5,10, 12 143:5,6,14,17,19 144:12, 17 145:3,13,19,21 146:2,15, 21 147:1,9 148:14 149:7,11,</p>	<p>17,21,22 150:13 151:1,2,6,9, 14,15 152:3,7 153:1,7,19 154:4 155:2,4,17 156:4,6,6,10,18, 22 157:16 158:17 159:3,8 160:11,12 161:8 162:4,20,22 163:19 164:10,22 165:13 166:7 168:16 169:20 170:2,7, 10,22 171:7,11,13,19 172:1,2, 4,17 173:3,17,18,21 174:8,19, 22 176:5,9 177:9 178:3,11,12, 13 179:3,11,12,13,15,19 180:3,5,6,11, 15 181:5,10,15,17, 18,19,20 182:2,12,15,20 183:1 184:2,5,7,8 191:8 192:12, 14 193:21 194:22 195:2,3,14, 17 196:2,3,4 197:7,10,13,16, 22 198:2,11,12,15,16,17,19 199:3,4,19 200:2,3,8,12,20 201:10 202:20 203:3,16 205:2,16,22 206:4,7,8,12,13,14 207:9,15,22 209:3 210:3 211:15,20 212:3,5,7,8,9,12,15 214:5 215:2,18,19,20 216:3,7, 9,12,12,13,14 217:3,11 218:7, 7,8,9,16,21 219:6,17,19 220:1,3,6,7,8 222:4,7,11 223:4 224:10 225:13,18 226:2 227:18 228:2,14,20 229:11,16 230:5,12,22 231:8,22 232:3,3, 4,14 233:2,5,6,12 234:3,6,12, 17 235:3 236:2,5,10,10,13,15, 18,20,21 237:3,6,7,7,15,19, 19 238:1,2,6,6,6,9,11,15,15, 18,19,21 239:2,5,6,9,12,13, 17,17,19,19,20,21,22 240:2,4, 4,5,5,5,11,12,13,15,17,18,20 241:4,5,9,12 242:2,3,5,10,11, 19,19 243:12 244:5,6 245:5, 16,17,20 246:9,21 247:4,12, 13,21 248:3,19,19,22 249:3,4, 7,7,8,18,19,22 250:2,9,16 251:19,22 252:6,9,16 253:20 254:10,22 255:19,21 256:4 260:10 261:4 262:7 265:14, 19 266:16 267:3,6,15,16 268:10,22 269:13 270:5,5,12 271:14 273:18 274:2,10,20,21 275:12,16,19 276:2,11 278:1, 13 279:15,17 280:2,4,5,10 281:3,20 282:17,17,21 285:13,14,19 286:4,8 287:2,5,5,6,7,7,12,14,16 288:11 289:22 290:2,5,12,15 291:3,9,22,22 292:7,7,11 293:22 294:2,13, 14,15 295:2,7,19 296:5 297:9 298:18,21 299:4 300:5,6,8,11, 13,14,18,20 301:15 302:20 303:7,12,12 304:4,11,13,14, 20,21 305:7,8,12,14 306:4,10, 12,15 307:1,4 308:3,9,9,10, 14,16,17,18 309:1,1,2,8,12, 17,18 310:3,8,18 311:12,13, 14,18,22 312:9,16,17 313:7,8, 13,14 314:11,15 315:1,2,8,10, 12,14,18,20 316:6,6,10,11, 13,17 317:2,16,18,21 318:4,5, 6,20 319:3,4,7,9 320:11,12,</p>	<p>19 321:9,16,17 322:13 323:6, 11,20 324:2,5,6,12,18,21 325:1,4,5,15 326:9,9,11,13,16,19 327:16 328:2,4,8,9,13,18,19 329:2 330:2,10,11,12,14,21 331:12,13,15,18,22 332:3,5,6, 7,7,8,9,14,15,17 333:5,6,7,10, 10,13,15,16,18 334:2,5,6,9, 12,15,20 335:2,4,7,8,11,13, 15,18 336:11,13,14,15,17,19, 19,19,20 337:11,14 338:5,8,9, 10,11 339:9,12,13,16,17,19, 21,22,22 340:10,15,20,21 341:1,2,4,7,12,17 342:8,11, 12,14,18 343:1,3,4,5,9,11,13, 13,17,21,22,22 344:12,17,20 345:5,13,19 346:2,15,18 347:2,3,19 348:1,5,5,8,10,11,12, 17,19,21,22 349:2,6,6,8,8,11, 12,18,21 350:1,9,12,13,14,15, 17,19,19,20 351:3,9,12,15 352:2,3,10,11,12,13,14,18,21 353:7,11,12,13,14,17,18,20 354:5,16,21,22 355:4,6,9,14, 19 356:13,17,17 357:13,14, 15,17 358:1,1,8,12,18,18,19 359:4,5,9,9,11,18,19,20 360:2,5,6,7,10,11,12 361:4,8,13,18 362:11,12,13,17,19,22 363:3,11,16 364:16,21 365:8, 9,15,17,22 366:3,6,8,8,9,17, 21 367:1,3,13,14,20 368:2,9, 19 369:4,5,15,22 370:3,3,6,6, 9,14,19,19 371:3,14,15,16,20 372:6,7,9,19 373:1,3,6,18,22 374:1,3,3,5,7,19 375:5,6,7,16, 17,18 376:2,6,13,15,15,19,22 377:3,15,18,22 378:4,12,12, 14,20 379:2,4,5,6,12,15,16, 18,20,20 380:5,8,18,20 381:5, 7,12,16,17,22 382:4,12,12,14, 15,19,20,21,22 383:1,1,3,6, 10</p> <p>That's ^[6] 306:6 308:11 312:10 325:19 337:17 358:11</p> <p>THC ^[3] 50:12 52:18 196:6</p> <p>the ^[3455] 3:16,25,29 4:12 5:4, 6,10,11,14,15,15,16,16,18,21, 22,22 6:1,6,6,7,5,12,13,14,17, 20 8:1,5,9,11,15,16,17,17,19, 20 9:11,13,16,19,19,20,22,22 10:1,2,4,18 11:2,5,8,11,17,18, 19,21,22,22 12:1,2,5,7,7,8,8, 9,9,11,15,18,22 13:1,3,8,9,12, 12,13,14,18,18,21 14:4,6,8, 11,16,20,21,22 15:15 16:5,9, 9,12,18,19,22 17:4,5,12,14, 16,17,20 18:1,6,6,10,10,12, 13,17 19:1,2,2,6,9,18,22 20:1, 3,3,7,8,8,10,18,18,18,20 21:2, 7,16,19 22:3,9,19 23:3,4,5,7, 11,11,12,14,16,20,21 24:1,1, 2,3,5,6 25:4,5,8,11,14,15,15, 18 26:4,5,7,11,13,15,16,22 27:2,3,6,9,10,12,21,22 28:2,7, 11,13,15 29:2,5,6,7,10,15,22 30:3,3,10,10,11,11,12,17,21,</p>
---	--	---	--

22 31:9,18 32:12 33:17 34:1, 2,6,6,10,12,13,13,16,20,21, 21 35:3,8,11,14,20,21 36:2,8, 13,13,19,21 37:2,2,3,3,4,6,6, 7,14,15,16,18,21,21 38:3,3,4, 4,6,7,7,7,8,8,9,10,12,17,18, 18,21 39:4,10,11,18,21 40:2, 2,3,7 41:3,3,3,6,9,9,12,12,13, 15,16,17,19 42:4,5,12,12,14, 15,16,22 43:1,1,2,6,9,12,13, 14,16,17,21 44:1,1,4,5,5,8,10, 11,12,13,14,16,18,19,21,21 45:3,5,5,8,9,10,10,11,11,15, 15,17,22,22 46:3,3,3,5,5,6, 8,9,10,12,16,21,22 47:1,6,10, 11,14,20 48:1,2,2,4,9,11,12, 17,20,21 49:3,4,7,8,14,16,22 50:2,3,5,5,9,10,10,11,12,15, 16,20 51:5,5,7,9,11,16,20,22 52:5,6,8,17,22 53:3,6,7,7,11, 12,19 54:2,2,4,8,8,10,13,22 55:1,9,14,15,16,17,18 56:9, 10,11,18,22 57:2,4,5,11,16, 19,20 58:3,5,6,6,8,14,21 59:2, 6,13,16,22 60:3,5,9,14,15,17 61:1,2,2,6,8,9,13,15,18,19 62: 6,9,13,15,21 63:2,6,9,16,20, 21,21 64:3,5,8,10,13,14 65:4, 7,14,21 66:5,6,8,9,10,12,13, 15 67:1,4,9,12,15,21 68:4,15, 16,17,18 69:4,5,9,11,12,15, 16,18,19,20,20,21 70:2,6, 10,10,12,22 71:6,7,8 72:1, 2,2,3,13,13,16,20 73:2,3,4,6, 7,12,17,18,19,21,22 74:14,15, 16,19 75:2,4,6,8,14,15,16,18, 22 76:14,14,15,20,22 77:1,8, 9,13,14,17,18,21,22 78:4,7,9, 10,10,16,19,21,22 79:1,3,5,6, 7,7,9,11,11,12,13,18,20,20, 21,21,22,22 80:1,2,3,8,8,9,10, 11,15,15,18,18,21 81:5,6,8, 11,12,13,13,15,16,16,17,17, 18,18,22 82:3,5,6,8,10,12,14, 16,20,21 83:2,2,4,4,6,7,8,10, 11,14,14,16,17,19,21,22 84:6, 6,7,14,14,15,19,20 85:9,13, 21,22,22 86:7,7,10,15,18,19, 20,21,21 87:1,4,4,5,6,12,13, 17,18,19 88:5,7,16 89:1,1,2,3, 5,6,10,11,13,14,15,16,17,18, 19,19,20,20 90:3,3,4,5,6,8,9, 11,11,12,13,14,15,16,20,20, 20,21,22,22 91:1,1,2,6,13,14, 14,18 92:12,13,17,18,19,20 93:3,9,12,12,14,17,18,19,21, 22,22 94:1,4,12,15,15,21 95: 1,2,4,8,9,13,16,18,19,20,21 96:1,2,3,7,8,8,10,12,13,14,16, 18,18,20,22 97:2,3,7,10,11, 20 98:3,4,10,14,15,19,22 99: 3,4,10,10,13,14,17,18,22 100: 6,8,12,13,15,15,22 101:8,9, 13,13,14,15,15,18,19,20,22 102:1,2,4,4,5,10,11,12,17 103:2,2,3,4,5,5,8,8,14,18,18, 20,21,21 104:3,4,6,7,9,12,18,	19,22 105:2,3,9,12,13,16,17, 21,22 106:2,3,5,5,5,6,11,14, 15,16,17,18,20,21 107:10,11, 16,16,22 108:6,6,9,11,14,15, 15,21,22 109:2,2,4,7,8,12,17, 17,19,21 110:6,12,18,19,22, 22 111:3,3,7,7,8,9,10,11,17, 18,20 112:4,7,9,11,11,12,13, 15,16,17,20 113:1,1,5,6,6,12, 16,18 114:1,3,5,5,6,8,9,10,10, 11,11,13,15,16,17,18 115:1,2, 5,8,8,11,12,13,14,15,17,20, 21,21,22 116:1,3,3,4,5,6,7,8, 8,10,10,12,13,14,19,20,20,22 117:3,4,4,6,6,8,10,12,13,16, 17,21 118:2,6,9,12,16,18,21 119:1,1,2,4,5,7,10,12,14,14, 15,20,22 120:1,3,4,6,7,9,9,10, 11,13,13,14,15,15,19,22 121: 1,3,5,8,9,9,9,13,14,16,18,19, 21,22 122:7,11,12,15 123:3,4, 7,7,10,11,17,22 124:3,7,8,9,9, 13,14,15,18,19 125:1,10,15, 15,19,20 126:3,8,9,10,10,14, 14,19,19,22,22 127:1,2,2,4,6, 8,14,15,16 128:4,4,7,10,11, 13,14,17,20,20,22,22,22 129: 1,2,5,12,12,13,21 130:6,8,10, 11,13,13,17,17,18,18 131:1,2, 2,3,4,5,9,11,12,13,15,16,18, 21,22 132:2,3,6,6,7,8,11,12, 12,13,14,14,16,17,18,19 133: 1,4,4,12,12,16,17,18,19,21 134:4,6,9,9,18,20,21,22 135: 2,5,6,10,10,11,15,15 136:1,1, 2,3,4,5,8,9,10,11,13,20 137:1, 4,8,12,14,18,19,21 138:3,5,5, 7,8,10,10,13,14,16,17,21,21 139:1,5,7,8,9,11,11,13,14,18, 20,21,21 140:3,4,7,8,10,13, 16,17,18,22,22 141:5,6,6,8,9, 13,15,16,20,20,21,21,22,22 142:1,2,3,5,6,8,9,9,10,10,11, 18,20,21 143:7,8,13,18,19,22 144:3,8,10,11,19 145:2,3,3,6, 7,7,10,11,15,20,21,22 146:5, 8,10,13,14,15,17,21 147:4,9, 10,11,18,19,21,22 148:1,2,3, 3,5,6,8,13,13,14,15,19 149:2, 6,6,8,9,10,10,12,12,13,14,18, 18,22 150:4,8,9,12,12,12,15, 16,17,18,21,22 151:5,9,10,11, 14,16,20,21,22 152:4,4,8,8,9, 10,13,13,18,19,19 153:2,7,11, 13,14,15,17,18 154:2,3,4,4,9, 10,10,11,14,16,16,17,17,18, 18 155:3,3,5,5,7,9,17,18,19, 20,21 156:2,3,6,8,9,12,13,14, 14,16,17,17,19,20,21 157:2,3, 5,5,6,7,7,8,12,13,15,15,16,17, 21,22 158:1,3,4,5,5,6,8,9,13, 14,19,21 159:2,3,3,8,14,17, 19,22 160:1,4,5,5,7,16,19,21 161:4,9,10,11,12,14,15,19 162:1,2,4,5,7,7,8,20 163:3,8, 10,11,11,14,14,15,19,21 164: 2,5,6,7,10,12,13,13,15,18,19,	21 165:5,5,7,8,10,15,16,17 166:3,7,12,13,14,15,15,18,19, 22 167:5,5,7,9,10,22,22 168: 4,8,11,14,15,15,17 169:4,4,6, 6,8,12,16,18,19,20 170:3,12, 14,17,17,18,21 171:9,10,11, 13,14,16,20 172:3,5,6,7,8,8,9, 13,17,18,18,21 173:2,3,4,8,9, 12,14,15,18 174:1,4,8,9,12, 13,15,15,16,18,20,20,21 175: 8,9,11,11,12,13,16,19,20,21, 22,22 176:1,1,4,6,8,11,12,12, 13,16,17,18,18,19,20,21,22 177:1,2,4,6,7,9,11,13,13,21, 22,22 178:3,6,9,13,14 179:6, 6,7,9,9,13,13,16,17,19,20 180:6,9,14,18,18,19,20,20,22 181:1,5,6,10,15,16 182:4,8, 10,11,11,13,17,20 183:2,8,13, 16,17,19 184:6,6,10,14,15,17, 19,20,21 185:5,7,8,9,13,14, 14,15,21 186:3,3,7,8,10,11, 14,17,17,19,19,22 187:1,3,5, 7,10,11,13,14,15,18,20,20,21 188:2,6,15,16,16,16,18,19,20 189:6,7,9,10,12,12,13,13,18, 19,20 190:2,3,4,7,10,11,14, 14,22 191:1,4,4,6,6,7,12,15, 18,21,22 192:4,6,9,10,12,22 193:5,6,8,11,12,19 194:4,4,6, 7,7,9,9,11,17,18,18,21 195:3, 5,13,14,15,15,18,19 196:3,4, 4,5,8,12,13,14,16,20,21 197: 5,11,13,14,14,15,17,18,19 198:2,3,5,6,6,9,11,13,16,18, 19 199:1,4,9,10,11,12,18,22, 22 200:3,8,9,12,13,14,17,19, 21 201:1,2,3,7,8,9,10,10,13, 13,16,16,19,19,22 202:3,3,6, 7,11,12 203:3,3,5,10,11,12, 15,17,19,20,22 204:6,10,15, 15,16,16,20 205:1,2,3,6,7,11, 14,17 206:1,2,2,3,4,5,6,7,10, 12,14,16,17,21 207:1,3,7,7,8, 12,14,16 208:3,4,5,7,7,11,12, 13,13,15,16,18,19,20,20,21, 22,22 209:2,4,6,9,10,12,12, 16,20,22 210:1,4,5,6,8,12,18, 19,22 211:1,2,5,6,9,10,13,13, 14,16,16 212:5,6,7,7,9,9,10, 12,17,18,19,20,21,22 213:1,4, 4,5,5,6,7,15,16,18,21 214:3,7, 8,11,15,18 215:2,4,5,6,9,10, 11,15,16,18,19,22,22 216:12, 13,20 217:7,11,15,17,19 218: 14,17 219:1,7,12,12,13,15,18, 18,19,19 220:1,6,11,13,17,17, 19,22 221:4,5,7 222:2,3,5,6,9, 10,11,16,16,19,19,21 223:1,2, 3,5,8,10,11,12,15,18,19,20, 21 224:2,2,4,9,12,13,17,19, 20,21 225:2,5,6,9,9,11,14,17, 17,18,19 226:5,6,6,7,8,11,12, 13,16 227:3,3,4,5,5,7,9,9,10, 13,15,16,18,22 228:1,2,2,4,5, 8,8,9,12,12,13,14,16,18,19, 20,20 229:5,15,16,17,17,18,	19,20,21,21,22 230:1,2,4,6,6, 13,18,22,22 231:1,1,2,5,9,9, 16,19,21 232:2,7,9,10,14,16, 22 233:2,4,7,8,12,16,17,20, 20,22 234:2,6,7,9,11,12,15, 17,18,19,20 235:5,8,9,12,13, 13,17,20 236:4,15 237:3,7,8, 10,11,12,14,16,17 238:11,12, 13,14,15 239:8,11,11,14 240: 16,17,18,19,20 241:9,18,20, 22 242:4,9,10,12,14,16,16,16, 17,17,18,20 243:2,8,11,12,16, 16,18 244:1,1,3,7,8,13,14,15, 17,19 245:3,7,21 246:2,3,4,5, 9,9,10,13,18,21,22 247:1,5, 11,11,13,13,13,14,17,18,20, 21 248:2,2,4,4,6,7,9,12,14,16, 19,19,20,20 249:1,1,6,9,12, 13,13,14,14,16,18,19,19,21, 22,22 250:1,3,4,4,7,7,7,8,9, 10,11,16,16,17,17,19,20,21, 22 251:3,4,10,12,16,17,19,19 252:4,5,8,8,10,12,16,19 253: 4,12,16,20,21,21,22,22 254:1, 2,11,12,13,15,18,19,22 255:1, 5,6,6,12,13,15,17,21,21,21, 22 256:2,4,5,8,9,11,14,15,17, 19,20,21 257:8,8,9,9,11,14, 15,15,16,20,20,22 258:1,2,2, 5,9,9,12,12,17 259:1,4,4,5,7, 10,10,12,15,16,16,16,17,19, 20,21 260:8,9,11,13,13,17,20 261:2,4,5,7,10,15,16,18,19 262:3,6,13 263:2,5,7,10,20 264:1,7,13,14,15,16,17,21,22 265:1,6,10,11,12,13,13,15,15, 17,19,22 266:2,6,6,8,12,15, 19,19 267:4,8,9,12,16,18,20, 21 268:8,10,11,12,16,17,18, 19,20,20 269:3,5,5,7,11,12, 15,20 270:2,5,6,8,9,13,15,15, 18,18,21,21,22 271:2,5,7,8,9, 13,14,16,18,19,21,22 272:1,1, 2,3,12,13,16,17,18,19,20,21 273:7,11,16,17,17,18,21 274: 5,8,12,13,14,14,19,22 275:4, 6,10,12,15,15,16,17 276:2,3, 4,6,8,9,11 277:1,3,4,5,12,15, 16,22 278:3,4,5,6,6,11,13,14, 15,21 279:3,5,6,11,14,16,20 280:4,9,17,17 281:5,6,7,8,15, 17,21 282:1,8,12,14,15,18,20 283:4,5,13,17,19 284:2,3,4,9, 10,11,12,14,16,20,21 285:7,7, 8,11,11,13,14,14,15,18,20,20, 22,22 286:3,9,10,14,15 287:2, 3,6,6,8,10,16,19 288:7,16,17, 21,22 289:11,12,13,14,14,15, 16,18,22 290:8,13,16 291:2,3, 3,4,10,11,12,14,14,15,17,17, 18,21,21 292:2,6,8,8,9,10,11, 13,14 293:5,7,12,14,15,19,22, 22 294:3,5,6,12,16,19,19,21, 22 295:1,2,9,11,13,16,17,18 296:3,7,10,13,14,16,18 297:3, 10,10,11,14,20 298:2,4,8,10, 11,13,15,16,19 299:9,10,12,
--	--	---	---

13,14,18,21 300:6,7,9,11,11, 12,14,18 301:5,5,5,6,8,10,13, 16,18,20,22 302:3,3,6,7,8,10, 17,20 303:2,6,8,8,11,16,22 304:1,2,9,12,13,14,16,20,21 305:1,2,3,4,7,12 306:5,7,7,10, 15,22 307:10,11,16,19 308:5, 6,8,17,21,22 309:2,4,8,10,10, 14,14,16,20 310:1,4,4,7,7,8,9, 10,12,15,16,17,19,20,21,22 311:7,9,12,13,14,18,19,20,20, 22 312:1,3,4,6,9,10,14,15,17, 19,21,21,21 313:3,4,8,9,14, 17,19,20 314:2,4,8,11,16,20, 20,21 315:2,2,13,19,20 316:1, 6,8,11,12,18,19,19,20,21 317: 1,4,5,9,11,17 318:3,14,21,21 319:1,15,22 320:1,5,5,8,9,9, 10,12,12 321:4,11,12,14,20 322:5,6,11,12,13,14,16,18,19, 20 323:1,4,5,10,12,15,20 324: 1,3,9,10,17,17,18,19,22,22 325:3,5,6,6,8,10,10,12,15,18 326:1,3,4,11,12,13,13,18,19 327:1,3,3,4,6,7,10,12,14,16, 16,20,20,21 328:1,3,4,4,5,6,6, 8,9,9,17,20 329:1,1,6,9,9,20, 22,22 330:2,5,8,11,12,14,16, 16,18,20,21 331:1,3,4,5,10, 12,14,14,18,18,20,21 332:1,1, 2,6,11,16,19,19,20,22,22 333: 3,3,15,19,19,20 334:4,5,11, 15,15,18,20,22 335:3,6,11,12, 15,17,19 336:2,4,5,7,7,11,14, 15,15,16,17,20 337:2,3,5,7,9, 9,10,11,14,14,15,17 338:5,6, 8,9,13,17,17,18,19,19,20,20, 21,21,21 339:2,3,4,5,5,6,8,12, 12,14,18,20,21 340:5,7,17,19, 20,21 341:5,5,7,10,17,18,19, 20,22 342:4,16,17 343:3,5,8, 10,12,13,14,17,17,19 344:2,4, 5,5,7,8,9,10,11,13,14,14,15, 16,18,19,21 345:1,2,5,6,10, 10,12,12,15,16,17,19,22 346: 1,1,3,4,8,10,17,18,21 347:3,9, 9,15,17,20,21,22 348:2,2,5,6, 6,7,8,8,9,11,12,13,14,18,22 349:3,3,4,8,10,18,19,20 350: 4,8,14,14,15,19,22 351:5,5,7, 14,16 352:2,3,8,13,15,16,16, 16,17,17,19,20 353:2,2,7,8, 10,12,12,13,13,14,15,20,20 354:9,12,14,18,20,21,22 355: 5,6,6,9,9,22 356:6,16,17,19, 21,22 357:1,5,5,7,9,9,10,10, 11,16,20,22 358:3,4,6,8,19, 19,22 359:6,7,10,11,14,17,20, 21 360:3,4,4,4,5,7,9,9,12,17 361:1,3,8,13,15,16,17,18 362: 7,7,9,10,18 363:3,9,10 364:4, 14,15,15 365:4,7,12,15,21,22 366:1,2,2,4,7,10,12,13,15,18, 18,21 367:1,2,7,8,8,11,12,13, 14,14,20,21,22 368:1,2,3,4,6, 9,12,16,18 369:1,2,5,5,5,13, 14,15,18,21 370:1,3,3,14,21	371:7,8,8,8,10,10,11,12,14, 21 372:1,3,4,5,21,21,22 373: 2,3,7,10,13,15,16,16,17,20, 21 374:1,4,7,7,8,13,17,17 375:4,5,8,9,9,14,14,21 376:2, 16 377:14,16,17,19 378:1,3,5, 6,11,13,21 379:1,3,3,5,11,12, 12,14,18 380:2,3,8,14,17 381: 3,10,12,20,21 382:4,6,7,9,9, 15,21,22 383:7,7,8,10,12,13, 13,14,16 384:21 385:5,6,10, 12,17,17,17,21 their ^[80] 10:1 14:8,9 16:3 20: 9 22:15,16 27:19 50:17 51:6 63:17 70:18 71:10 77:10,14, 16 79:14 82:1 84:18,21 85:3 86:9 97:1 101:5 111:17 135: 8 144:15 146:2 147:6 148:15 149:8 150:17 151:21 152:1,9, 12 153:20 154:19,21 161:6,7 168:1 171:20 173:11 174:5,6 176:15 177:8,15 184:13 185: 2,13 189:2 229:20 236:19 240:15 241:20 246:8 252:1, 13 262:8 263:4 273:10 275: 21 279:18 280:20,22 281:14 288:2 294:8 299:19 317:21 321:13 333:1 353:6 357:2 358:20 363:21,22 370:4 them ^[55] 14:2,11 21:3 24:9 56:20 59:10 94:8 113:13 128: 9 133:3,17 135:8 143:9,13 144:5,14 145:15 146:1 152: 12 153:3,3,4,5 161:15 173:1, 11 216:5 246:6 251:4 275:13 294:7 300:1 303:11,16 316: 15 318:16,16 320:11,18 321: 1,2,5 331:15 341:2 343:11 351:4,9 353:8 355:11 356:14, 15 361:2 380:14 382:7 385: 16 theme ^[2] 130:22 277:22 themselves ^[1] 22:16 themselves ^[8] 10:1 24:10 71:7 184:15,18 196:10 240: 12 363:14 then ^[75] 11:16,22 20:21 21:2 23:5,7 28:17 31:5 36:3 37:20 49:22 50:4 56:20 66:1,6 69: 13 89:19,22 90:4 94:2 110:2 112:3 132:17 133:13,17 146: 10 149:15 150:8 154:3 165: 15 172:1 173:17 185:6 186:6, 9 192:22 193:5 222:4 224:17 241:1,21 247:2 251:18 262: 21 263:4 271:22 276:10 278: 10 282:20 300:21,22 302:10 303:21 307:6 317:4,10 318:3 325:21 327:3 329:8 330:18 336:3,3 337:13 350:14 355:2 365:12 367:4 371:9 373:21 374:12 376:14 379:4 382:19 383:11 theoretic ^[1] 268:21 theoretical ^[1] 368:21 theory ^[1] 28:6 therapeutic ^[28] 32:5 41:5 50:	6 68:16 73:2 126:19 134:6 148:18 190:3 205:17 206:5, 11,21 207:3,4 208:6,11 211:1, 6 212:1,6,11,22 213:12 214: 21 247:17 248:1,20 therapies ^[3] 92:10 99:21 154:12 therapy ^[38] 47:17,22 48:5 73: 7,7,13,14 87:9,14 100:2 102: 13 103:3,6 104:6,9,16,17 105: 6 107:12 108:5 123:13,16 125:20 129:7 135:15 139:18 140:13 146:19 147:17 148:2, 9 150:9 180:22 181:22 245: 10 290:19 365:9,10 there ^[277] 18:21,21 20:10 22: 13,20 23:22 24:4 26:3,9 27: 11 28:17 31:3 34:8,19,20 40: 13 58:19 62:22 75:4 78:6 82: 16 83:5,21 86:11,22 88:2 96: 6 97:14 99:12,15 100:2 102: 8 103:14,15 104:9,9,11,12,20 105:7 106:1 107:2,15 109:20 110:16 112:17,18 113:3,4 115:7,10 118:1 119:4,9,20 120:7,14 121:19 122:2 123: 15 124:18 125:1,22 126:12, 14 127:1,1,8,9,11,18 128:3, 11 130:16 132:7 133:10,14 134:7,11 135:17 136:16 137: 2 139:22 140:9 141:12,22 145:8 148:2 149:5 150:11 151:19 152:7 153:16 155:16 161:17 164:22 165:2 168:19 170:10 171:15 174:12 176: 18 178:4,20,21 179:2,7,22 180:5 183:15,21 184:2,14 188:22 190:12 191:17 195:1 196:1 197:22 198:17,21 199: 7 207:22 208:14 209:20 210: 10,12,15,17 214:2 216:3,16, 18,19 217:2,5,13 218:6,16 219:17 220:13 225:16 226: 10 229:16 231:10,22 233:16 236:1,16 237:6,22 239:22 240:19 241:14 242:2 246:21 247:4 248:18 249:3 253:18 254:3 257:12 267:2,21 272: 10 274:10 278:17 279:10 284:13 285:15 287:14 290:5 292:22 295:14 296:14 297:8 298:1,3 301:6 302:12 303:14, 15 304:4 305:5,11,12,18,22 307:5 308:14,15,22 309:11 311:9,10 312:16 313:8 317: 17,19 318:15 319:2,5,8,10 320:15,19 321:8 322:22 323: 1,17,17 324:8,20,21 325:2,18 329:21 330:9 332:3 334:1 336:10 340:10,12 341:11 342:7,14,18 348:19,22 349: 12 351:18 352:5 353:4 354: 10 355:2,8,10 356:7,8,12,16, 17 357:4,16 359:4,20 360:1, 10,19 362:9 363:8 366:9,16 367:6 368:15 369:19 373:17, 18 374:1,18,21 375:9,11,11,	12,22 376:11,14 379:19,20 381:11 382:10,19 385:1,4,15, 19 there's ^[1] 363:4 thereby ^[1] 169:15 Therefore ^[13] 57:7 81:4 87:8 107:22 112:7 116:10 161:10 172:19 274:5 335:10 340:14 365:1 378:22 these ^[212] 5:17 10:15 12:16 17:11,13,16 18:11 19:19 20: 7 21:9,20 22:7 23:3 24:5 27: 5,6 28:3,19 31:7 32:16 33:12, 14 34:22 35:16 37:10 38:6, 12 39:7 43:7 48:8,13 52:12 53:10 54:21 59:8 64:2,16,19 65:2,18 67:12 71:5,14 75:18 76:19 78:2,14 80:14 81:12 84:1 92:6 93:19 94:7 95:7,21 96:17 97:5,16,21 102:16 104: 14 106:1 107:1,9,21 109:7 110:6,9 111:3 113:8,11,17 117:17 120:2 123:2 131:16 132:17 136:21,21 140:16 141:8 142:14 148:10 152:5 155:11 156:11 159:10 161:5 163:16 164:1 166:2,4 171:4, 18 172:6 175:11,16 177:7,11 179:8,11,17,18,22 180:3 182: 15 187:2,21 189:16 190:13, 18 192:1 194:19 195:21 199: 1,4 201:4 205:1 206:13 207: 15 211:22 218:2 220:8 224: 21 226:9 227:4 229:2,10 231: 4,8 233:6 234:2 243:18 249: 2 253:19 254:4 261:15,22 265:10,20 266:9,11 268:18 271:6,11,18 272:11 273:7 275:7,10 280:14 281:12 282: 2,2 283:6 286:19 290:20 291: 19,22 293:5 294:2,5,20 295:1, 12 296:10,13 297:21 299:15 302:9 306:18 307:1 309:7 312:3 319:6,7 322:10 329:7 331:4,9,14 332:17 333:4 334: 17 335:5 341:6 342:1,9 351: 2 355:13 356:13 358:20 360: 8 361:6 363:15 365:7 366:19 369:18 371:2,4,18,21 372:5,6, 8,15 374:6 375:15 376:21 377:2 380:12 381:6 they ^[227] 10:4,6 16:21,21 18: 19,19,20 20:13,15 22:14,15, 16,17,21 23:6 24:8,10 25:21 26:7,9 27:16,18 28:7 33:12, 17 34:1,11 40:4 48:12 50:22 51:1 60:5 63:16 65:12 66:4 75:2 77:15 85:1 96:20 97:2 98:18 100:8 103:15 105:5 113:2 121:13 130:10,20 136: 20 143:13 144:16 145:2 148: 1 149:8 153:1,12,18,19,20 154:9 161:15,22 165:7 167:8 170:2,21 171:22 172:1,2,2,5, 22 173:10,12 174:4,4,5,5,21 178:16 179:18 180:13 181:3 182:16 184:1,4,17 187:3,5
---	---	--	--

<p>188:7,9,18 189:5 192:16 200:8 203:11 216:15 218:9,20 219:9 224:16,18 227:6 229:1 232:4 234:4 235:2,3 236:19,20,20 237:3 238:17 239:3,10,16,20 240:14,22 241:4,18 242:18 250:18 251:4 254:6 261:5,6,17 262:2 265:3,18 275:3,4 291:20 294:8 296:14,17,19 300:9 303:3,18 304:14,15 305:5 306:2,13 308:8,21 309:1 311:22 312:1,18 313:15 317:21 318:6,7 319:17,17,20 320:15,16 321:14,16 326:5,6,7,8 338:10 342:2 33,6,9,10 346:4 347:4 348:7 350:2,3 353:14,15 354:16 357:3 358:5,21 359:13,14,16,16 360:2,3,5 361:14,17,18,19 362:15 363:17 364:1,5,7 365:11 368:19 371:7,9,19,19 372:2,3,3 374:20 376:7,7,9 378:14,22 379:2,7,13 380:3,5,18 381:13,13,13 385:7,12,12</p> <p>thing ^[18] 21:19 23:17,21 30:4 33:8 106:21 181:16 236:11 237:19 328:4 331:6 332:19 348:8 351:7 373:1 379:6,12,14</p> <p>things ^[32] 16:20 18:18,20 21:9 24:6 25:12 30:11,12 31:2,21 35:16 36:3,5 148:14 150:6 216:13 228:21 231:2,8 235:17 238:8 320:13 330:1,7 332:17 348:5 353:9 364:8 368:7 370:3 372:15 382:4</p> <p>think ^[168] 13:16 14:19 22:4 27:3 29:2 35:10 36:10 51:12 162:13 172:10 176:6 180:4 181:14 182:22 184:7 185:12 216:14 219:13,17 236:2 237:12,20 238:8,10 239:19 242:5 247:5 248:11,15 249:5,7,7 294:4 300:2,11 308:3,13 309:11,18,20 313:7 314:9 316:22 317:21 319:22 323:11 324:7,11 325:8,11,22 326:14 330:2 332:6 334:1,8,16 335:7 336:1,10 337:4,10 338:7,12 339:5 340:14 342:3 345:3 346:9 347:4,8,14,15 348:8 349:7,8,18,21 350:4,6,12,14,17,19 351:9 352:9,18 353:9,11,18 354:8,18 355:2,8,18,19 356:13 357:8 359:4,9,11,19 360:1,2,11 361:2,3,5,10 362:4,7,12,17,18 363:8 366:7,9,14,22 367:4,6 370:19 371:3,14,16,22 372:1,4,9,14,19 373:1,21 374:22 375:14 376:5 377:13,15,17,19,21 378:4,5 379:9,10,15,20 380:2,11,16,18 381:5,7,11,15,17 382:1,4,7,12,21 383:1 385:3,3,13,14,14,15</p> <p>thinking ^[12] 12:16 55:13 60:2 108:17 240:13 297:3 316:3 329:7 366:19,21 373:15 375:</p>	<p>22</p> <p>third ^[8] 12:22 104:6 118:21 159:8 176:4 198:11 255:5 363:4</p> <p>Thirdly ^[1] 328:8</p> <p>this ^[568] 5:6,18 8:18,22 9:2,5,12 10:17,22 11:7 13:15,20,15:12 16:8,14,16 17:11 18:9,10,22 19:8,10,15 21:19 22:3 23:13,16 24:10,15 26:6,11,14,18 27:2,8,13 28:18 29:5,7,11,15 30:6,17 31:21 32:19 34:1,10 35:4,14,19 37:7 39:5,19 40:11,21 42:5,6,13 44:18 45:14 46:13 50:14 51:21 52:22 54:22 55:16 56:7 57:5,16 58:1,7,11,16,18 60:18 62:19,20,22 63:18 64:4,8,17 65:13 66:3,14,20 67:3,14 72:9 74:19 75:3 77:14 78:9 79:17,21 81:6 84:8,15 85:5,5 87:3,6,14 88:4,19 89:5,12 91:6 93:11,17 97:10,18 98:12 102:19 103:1,12 104:20 105:1,1,21 106:9 108:6,14,18 109:3,12,15 111:7,9 112:10 114:8,15,16,17,20 115:12 116:11,18 117:3,11,14,17 118:7 120:1 122:13 124:3 126:8,9 127:5 128:16,19 129:2,18 130:5,14 131:11,16 132:8,22 133:4,13,22 135:9,12,18,21 136:4 137:12,14 138:3,6,16 139:19 140:9,21 141:2 142:3,6,7,19,22 143:20 144:22 145:6,12 148:13,21 149:1 150:3,11,14,20 151:17 152:14,17,17 154:1 155:2,8,9 156:9 158:7,13 160:7,8,18 161:2,3,17 162:13 163:13 166:6,11 167:5,19,21 169:11 170:21 171:10 172:7,14,21 173:14,18,18 175:4,21 177:3,14,21 178:1,19 179:8,14,19,20 180:1 181:14 182:7,7,8,10 183:1 187:3,22 189:21 190:7,10 191:8 192:11,14,17,21 193:2,4,14 194:13,14 195:4,13 196:2 197:1 198:7,16 199:18 200:13 201:2,3,13,15,19 202:20 203:3,5 204:6 205:9,11,16 207:8,22 208:3,18 209:11,16 210:5,18 211:1,4 212:4,11,15,17 218:13 219:4,12,14 221:4 222:3,9,15 223:1,7,14 225:12 226:2,9 227:3 228:4,7,16 229:2,11,12,17,19 230:20 231:19 232:5,11,16,17 233:6,14 234:1,5,15,16,18,22 235:22,22 236:2,14 237:6,15,21 238:4,8 239:5,7,10,12,15,18,22 240:2,7,11,22 241:2,6,7,8,15,17 242:3,5,12,12 243:3,22 246:10,19 247:6,8,9,12,18,22 248:3,13,15,18 249:1,2,12,17,17,21 251:14,20 255:8 256:4,13,17 257:2,3,22 258:6,7 262:1,6,12,17 263:2,</p>	<p>13,18,19 264:1,5,12,16,18,20 265:9,12,16 266:3,14,17 267:15,15 271:21 273:3 275:14 276:2,4,19 277:13 278:5,7 280:5,9 281:4 282:6 283:4,15,20 285:11,17 287:3,11,12,19 289:22 291:9,20 293:3 294:5,14,16,19 295:8,10,11,18 297:1,1,4 298:8,11 299:13,19 301:8 302:1,8 305:7 306:3,3,6,15 307:12 308:20 309:14 310:6 311:5 312:9 313:10,16,19 314:6 315:6,18 316:2 317:18 318:22 319:2,21 321:8 322:16 323:1,12 326:8,11,14 327:1,18 330:4,7 331:3,6,16,17 332:16 333:9,11,21 334:3 335:1,10,12 337:5,8 338:7,15 340:14 341:17 343:6,21 345:3,22 346:11 348:18,22 349:13 350:16 352:2 355:17,19 356:4,5,11 358:1 359:4 360:13,19 361:12,20 362:5,12,18 363:19,22 364:7,19,20 365:1,4 366:1,3 367:22 368:5 369:21 370:14,16,20 371:10,15 372:7,16 373:8,15 374:14 376:2 377:18 378:18 379:20,21 380:8 381:8,14,17 382:2,11,20 385:10,14,20</p> <p>Thomas ^[2] 2:6 14:3</p> <p>thorough ^[1] 234:8</p> <p>thoroughly ^[2] 45:10 48:21</p> <p>those ^[109] 20:12 21:3,15 22:1 28:9 30:5 31:2 35:17 36:3,4,5 48:1,3,4 52:5,7 59:1,7,12 79:9 87:15 96:12 97:1 115:1 126:18 129:1,21 130:17 131:8 140:18 143:11 146:8,10 147:13,14,16,20 148:7 150:7,21 152:21 153:6 154:15 156:17,18 157:9 161:8 162:11 167:1,14 169:10,13 171:3 172:19,20 173:10 184:7 186:10 189:10 194:6,8 196:9 203:7 206:17 209:3 214:4 237:17 250:19 251:3 252:15 254:18 255:14 257:19 263:11 277:3 279:14 281:9,12 289:12 290:12 295:9 304:15,19,21,22 307:5 313:4,5 314:13 318:9,11 320:17 323:18 328:14 330:22 333:11 341:11 353:9 354:17 355:7 356:21 358:2 359:22 360:16 361:22 364:8 367:4 372:11 383:8</p> <p>though ^[14] 24:4 41:2 55:4 85:17 142:17 145:17 151:12 177:22 229:1 241:8 251:3 331:2 341:10 381:18</p> <p>thought ^[17] 24:18,20,22 25:17 30:18 35:14 55:14 189:7 196:21 197:6 198:8 202:6 273:18 301:4 316:8 344:17 369:1</p> <p>thoughts ^[6] 11:19 24:16 33:12 288:2 310:10 369:14</p>	<p>thousands ^[2] 19:5,5</p> <p>threat ^[1] 16:20</p> <p>threats ^[1] 244:14</p> <p>three ^[28] 8:10 9:17 37:7 79:182:10 128:10 130:18 134:5,6 140:7,10,22 144:15 156:8,17 176:1 185:9 197:22 222:4 223:17 257:11,15 270:16 299:21 319:2 322:7 341:11 374:6</p> <p>three-fold ^[1] 282:1</p> <p>threshold ^[2] 82:6 269:12</p> <p>thresholds ^[1] 82:3</p> <p>throat ^[1] 302:19</p> <p>Thrombosis ^[2] 93:4,15</p> <p>through ^[49] 15:18 23:4 25:11,11 27:11 30:19 43:6 44:145:18 63:19 67:6 102:20 108:19 109:19 111:5 119:21 138:11 143:4 145:14,15 152:14 159:9 193:10 194:12 195:4 198:8 200:14 201:6 203:21 207:19 218:5 224:10 240:15 241:2 242:15,19 301:5 302:11 307:13 327:21 341:6 352:8 366:2 369:21 370:18,20 375:20 381:18 382:6</p> <p>throughout ^[5] 51:19 56:17 76:20 97:2 140:22</p> <p>throw ^[2] 230:9 312:16</p> <p>throwing ^[1] 337:5</p> <p>thus ^[23] 21:14 52:1 54:13 57:9 60:8,22 66:20 68:15 79:7 80:16 88:9 90:16 92:18 158:21 164:10 167:9 193:12 203:3,9 205:7 258:22 284:20 328:1</p> <p>tick ^[1] 374:19</p> <p>tie ^[1] 341:2</p> <p>tighter ^[2] 26:15 325:19</p> <p>time ^[57] 13:14 20:18 29:19 33:22 46:8 50:22 63:21 66:5 67:2 80:9 86:15,19 87:5 88:7 92:3 93:21 104:8 110:16 113:16 118:2 120:13 135:15 139:19,20 142:7,19 145:7 147:10 153:11 154:2 177:21 178:14 180:8 185:4,6 207:6 224:5 232:19,20,20,21 233:3 243:3 266:10 271:13 282:17 294:16 303:7 329:13 335:15 337:1 347:19 361:13 367:3 370:4 373:16,20</p> <p>time-dependent ^[1] 64:12</p> <p>times ^[13] 123:14 134:6 148:10 206:1,4,21 210:1 212:1 234:1 247:22 270:2 333:6 352:10</p> <p>tingling ^[1] 268:14</p> <p>tireless ^[1] 299:19</p> <p>tissue ^[10] 65:4 67:11 194:6,9 196:4 197:14 198:22 200:22 220:17 225:7</p> <p>tissues ^[6] 52:10,12 67:10 189:14,14 225:8</p> <p>to ^[1302] 3:2 5:2,3,8,8,8,9,12,16,20 6:1,5 8:17 9:1,5,9,10,</p>
--	---	--	---

11,22 10:3,7,9,15,15,16,17, 18,20,21 11:15 12:5,9,12 13: 5,13,15,17,18 14:7,9,10,16 15:10,14,14,16,19 16:2,4,5, 11,13 17:3,19 18:6,16,22 19: 9,15,15,17,18,20,20 20:8,13, 20 21:3,7,20 22:8,8,9,15,18 23:8,10,20,21,22 24:3,6,9,11, 16,16,20 25:5,9 26:15,19 27: 1,3,6,13,19,20 28:6,22 29:3,7, 10 30:7,10,11,12,18 31:1,5, 10 32:20 33:3,8,13,17,22 34: 8,10,10,13,15,22,22 35:1,14, 17,17 36:1,2,2,10,12 37:3,6,7, 9 38:10 39:5 41:16,20 42:11 43:17 44:17 45:11 46:4,8,13 47:2,3,11,12,20 48:14 49:2, 15 50:1,11 51:10,15 52:5,7,7, 16 53:7,11,14,19 54:4,5,8,15, 19 55:3,4,14 56:2,5 57:2,13, 14,16,17,19 58:4,11 59:9,18 60:9,16 61:2,18,20 62:1 63: 10,11 65:15,22 66:5,17 67:1, 2,12,15,21 68:18 69:1,12 70: 2,7,8,13,17 71:3,14 72:6,10, 19 73:8,11,18 74:3,6,8,14 75: 9,11,15 77:10,11,21 79:2 80: 8,11,14,15,17,22 81:2,8,16, 21 82:5,17,20 83:18,20 84:11, 12,18,18,19,22 85:1,10,13,17 87:6,8,13 88:19 89:1,11 90:1, 9,14,17,19 91:11,15,16,22,22 92:3,7 93:2,11,11,22 94:9,18 96:1,7,13 97:5,6,17,17 98:5 99:14 100:21 101:10,16,18, 20,22 102:1,4,5,7,11,12,12, 16 103:5 104:4,8,18,22 105:1, 2,12,19 106:1,6,10,18,19,22 108:7,16,17,22 109:20 110: 18,21,22 111:11,18 112:1,20 113:3,5,12 114:1,7,8,9,17,20, 21 115:3,5,6,14 116:1,21 117: 7,16,20 119:2,12 120:6,7,9, 18,22 121:2,8,9,14,20 122:5 123:10,11,14,14 124:2,10 125:3,11,20 126:2,2 127:5,7, 15 128:9,10,21 129:1,5,18,19 130:2,8,10,10,22 131:14,17 132:11 133:1,15,16,20 134:6, 14,19,20 135:8,9,9,14,16 136: 2,8 137:6,8 138:16 139:2,20, 21 140:3 141:13,14,15 142:4, 4,7,7,8 143:8,9,13 144:4,7,14, 15,22 145:2,9,12,14,15,15 146:14,15,17,18 147:10,11 148:1,2,4,6,14,16 149:2,17, 18,19,20,20 150:9,11,13,17, 17,18,20 151:1,2,5,7,9,20 152:12,13,20 153:2,4,20 154: 1,2,8,8,10,10,11,13,14 155:2, 8,8,12,16,17,21 156:4,4,7,8,9, 13,13 157:2,4,7,12,14,19 158: 6,13,15 159:11 160:17,19,21 162:4,14,15 163:7,19,22 165: 12,15 166:6,7,21 167:1,6,13, 18,21 168:8 169:4,9,13,19,22 170:11,13,17,20,21 171:1,12,	22 172:13,13,17 173:1,11,22 174:3,13,15,16,17,19,21 175: 4,8,18 176:2,16,19,21 177:1, 3,9,20,21 178:1,22 179:20 180:5,14,18 181:1,5,11,11,15, 17 182:1,6,15 183:6,11,15,22 184:8,14,17,18,21 185:2,3,5, 5,20 186:6 188:20 189:7 191: 7 192:1,2,20 193:3,6,8 194: 14 195:22 196:2,6,8,19,19,21, 22 197:6,7 198:1,8,10,15,22 199:7 200:1,6,9,10,10 201:4 202:6,19 203:1,7,12 204:16 205:17,19 206:12,21 207:3, 11,13 208:5,7,13 209:1,4,5,6, 12,18,22 210:1,11,12 211:9, 16 213:1,5 214:13 215:4,6 216:1,4,4,9,12 217:6,9,16,22 218:7,8,13 219:12,13,16,16 220:3,18,19 221:8 222:5,12, 15,18,20 223:3,12,13,17 224: 4 226:12 227:9,19,22 228:3, 11,14,17 229:1 230:7,9,16,17 231:5,8,21 232:4,7,14,15,20 233:9,15 234:6,14,19,21 235: 8,15,16,16,20,22 236:13 237: 4,5,8,9,10,15,17,17,21 238:1, 1,2,5,14 239:1,5,9,10,15,17, 19,20 240:10,11,13,13,14,15, 15,18,20 241:2,3,4,7,8,10,16, 17,22 242:9,10,18,19,21 243: 3,4,12 244:14,20,21,21 245: 13,20 246:6,7,8,13,18,19 247: 1,2,8,17,18,21 248:9 249:1,6, 20 250:1,13,15 251:4,13,17 252:1,7,17,22 253:1,7,18,19 254:1,2,5,6,10,13,17 255:8 256:2,8,18,21 257:6,17,18,18 258:3,22 259:5,9,11,20 260: 14,17,19 261:19,22 262:3 263:5 264:22 265:3,14,22 266:7 267:13 268:2 269:4,8, 21 270:2,2,17,21 271:8,10 272:6,10,19 273:1,18 274:10 275:1,7 276:3,4 277:2,11,12, 22 278:1,15,21 279:13,14,15, 15 280:9 281:13 282:2,18,18 283:1,12,17,19 284:1,2,3,21 285:18,22 286:9,13,19 287:5 288:2,19 289:3,10,10 290:4, 17,22 291:12,19 292:2 293:1, 7,15,15,20,20,21 294:4,7,11, 12 295:2 296:7,12,22 297:3,9, 22 298:3,10 299:3,9,12,17,17 300:1 301:4,8,21 302:1,9,9, 12,12,13,13,14,19,22 303:17 304:1,15 305:4,6,10 308:7,10 309:3,6,6,8,17,21 310:14,18 311:6,15 312:1,7,16 314:4,18 315:7,15,16 316:4,6,6,7,11, 13,18 317:3,6,11,13,14,22 318:6,7,10,13,20,20,22 319: 14 320:10,20,22 321:11 322: 12,12,13,15,16,16,19 323:4, 13,15,22 324:4,12,17,17,22 325:3,22,22 326:16 327:1,2,3, 6,7,7,15,17 328:13,18,22 329:	1,10,17,17,19 330:3,7,9,13, 21 331:1,4,10 332:2,6,7,7,8, 10,21 333:7,14,16,19,21 334: 6 335:11,12,17,18 336:4,16, 20 337:1,2,6,12,17 338:8,12, 13,16 339:1 340:4,4,16,16,17, 19 341:2,3,21 343:2,3,6,13, 14,17,17,18,22 344:6,7,8,11, 12,13,15,16 345:8,10,11,16, 19,21 346:7,8,11,17 347:1,4, 6,7,8,18,20 348:2,17,22,22 349:2,4,5,7,7,10,13,17 350:8, 10,10,11 351:7,17 352:2,7,13, 19,20 353:2,4,8,10,11,14,15, 21 354:14,19 355:2,3,11,17, 18 356:8,8,9,10,18,20 357:2, 3,8,8,10,14,17 358:13,16,17, 19 359:17,18 360:4,17,21,22 361:11,19 362:5,8,17 363:4,7, 13,13,15,21,22,22,22 364:18, 21 365:4,4,22 366:7,11,13,19, 21 367:4,8,9,10,12,19,21,22 368:2,11,13,18 369:1,4,10,13, 17,19 370:5,6,8,12,13,22 371: 1,3 372:8,10,13,15,18,18,21, 22 373:2,3,10,20 374:9,9,12, 13,14,16 375:3,8,10,15,17 376:9,18,22,22 377:3,4,14,14, 20,21,22 378:1,6,10,12,18,20, 22 379:1,5,6,6,7,10,18 380:2, 4,8,12,12,18,19,19 381:3,4,4, 5,9,15,15,20 382:2,3,5,7,22 383:5,5,6,6,7 385:4,5,6,9,11, 13,16,20 today [54] 10:14,20,22 11:2 13:15 14:2 20:4 26:2 27:4 32: 21 33:2 37:2,12 38:22 39:19 40:9,11 41:18 44:6,13,15 45: 1 46:2,11,12,21 47:18 48:7, 11 49:17 73:20 97:11 113:10 121:1,5 127:6 136:10 137:10, 14 139:11 140:15 185:20 189:11 190:6 235:16 251:12 283:2 297:19 310:3 312:10 330:1 337:12 367:15 369:16 Today's [6] 5:13 8:19 51:15 59:18 95:8 257:14 Todd [2] 308:4 324:15 together [16] 30:21,21 51:5 78:1 141:21 145:21 157:6 159:10 195:22 238:18 339:6 345:2 347:10 366:15 377:22 378:1 told [4] 144:8 280:10 365:9,11 tolerated [2] 75:13 135:4 Tom [6] 8:2 217:21 365:19,20 367:17 379:16 tone [6] 57:11,15 59:21 192: 10 207:17 211:9 tongue [1] 320:13 tonic [2] 210:8,12 tonic/clonic [1] 130:4 tonicity [2] 196:20 197:1 too [10] 183:9 240:18 294:6 305:16 326:15 333:11 349: 19,20 353:12 357:8 took [5] 18:4 46:8 115:17 129:	18 239:2 tool [10] 29:3 92:14 141:13 152:10,11,17,18 153:16 155: 2 383:3 tools [15] 57:19 140:16,19 143:14,19 145:20 146:10 147:20 151:2 152:9 153:5 156:18 168:8 196:14 246:8 top [6] 79:22 83:4 132:12 293: 14 339:18 370:2 topics [1] 39:18 total [23] 40:21 69:22 79:5 80: 17 97:11 208:6 253:13 270: 22 275:5,6 283:11 284:6,20 294:22 295:1,9,16,18 311:2, 21 315:13 318:14 325:6 totally [3] 31:19 64:22 331:6 touch [3] 200:6 218:13 219:4 touched [1] 323:12 toward [4] 210:13 274:12 285: 3 310:10 towards [9] 12:9 49:17 63:7 154:19 163:21 165:8 210:18 227:18 326:17 toxicities [19] 185:21 186:11 199:19 203:13 205:13 206:6, 8,15 212:3,10,12,18 213:2,7, 15,22 214:21 222:10 249:3 toxicity [17] 205:4 206:17 207:1,9 209:2 211:21 213:11, 20 214:5,8 224:19 230:17 231:11 246:22 249:18,22 323:18 toxicological [1] 134:1 toxicology [11] 186:7 204:7, 11,14,21 206:13 207:14 216: 20 217:11 218:4 269:21 track [2] 29:4 173:10 tracking [2] 31:11 155:21 tracks [1] 30:2 tract [3] 189:15 201:1 225:7 trade [1] 153:15 traditional [3] 188:8,8 192:12 training [6] 18:21 34:9,12,13, 16,19 tranquilizers [1] 227:13 tranquillizer [1] 227:2 transduction [1] 195:17 transient [6] 63:7,9 86:21 124:16 346:3 translate [1] 326:9 translated [1] 302:10 translates [1] 159:1 translation [1] 302:17 transmission [6] 58:2 192:4, 13 193:22 207:14 239:7 transparency [1] 222:18 transparent [2] 96:2 222:17 transport [2] 188:16 220:13 transportability [1] 26:1 transported [1] 220:16 trauma [1] 19:13 travel [1] 223:8 travels [1] 303:9 treat [19] 56:20 142:4 149:12 154:13 167:1 170:21 343:13, 14,18 344:6,7,12,15,16 345:
--	--	--	--

<p>11,20 347:7 377:16,21 treatable ^[1] 135:19 treated ^[31] 39:20 63:14 64:15 65:20 66:13 74:21 78:16 79:4 84:3 85:18 103:22 129:7,9 135:2 136:19 137:6,18 139:19 147:7,16 155:13 157:4 167:4 168:1 270:15 277:6 288:3 290:15 293:5 341:19 351:4 treating ^[4] 108:2,3 135:8 229:11 treatment ^[116] 29:4 31:14 32:13 37:4 38:18 39:12 41:4 43:18 44:11 46:17 50:6 64:17 66:3,20 68:12,16 69:13 72:2 73:3,18 74:10,17 75:3 77:9,11 80:12 81:3,18,20 84:17,18 85:9 88:4 89:7,22 91:17 92:7,20 96:4,11 103:5 104:4 107:14 110:19 113:18 116:2 118:4 123:10 127:21 128:22 137:22 141:19,21 142:11 146:20,21 148:3,13,16 149:9,10 151:21 153:19 157:7 158:4,6 160:16,19,21 161:5,19 162:5,11 165:21 166:4,13,16 167:7,21 169:7,19 173:1,15 175:22 182:16 190:4 199:21 208:20 211:7,14 228:3 243:18 245:1,8,11 255:11,12,15 257:18,20 258:3 271:5 273:8 277:5,11 281:1 283:16 284:10 286:18 289:18 309:22 316:5 325:16 351:1 357:1 381:21 treatment-group ^[1] 259:12 treatment-naive ^[7] 39:15 85:21 86:15 88:11 92:11 100:1 265:9 treatments ^[9] 158:18,19 159:18 161:8 166:14 172:22 245:4 281:17 356:7 tremendous ^[4] 236:3 314:3 324:19 385:15 tremendously ^[1] 171:21 tremor ^[23] 124:20 125:2 136:12 212:4 213:3 247:10 263:14 267:4 268:15 304:1,2,4,4,6,6,6,8,9 305:1,2,3,8,13 tremors ^[12] 200:4 202:4 206:3,3,9 208:1,10,15 247:15 248:8 305:5,6 trend ^[2] 210:13,17 trended ^[1] 278:22 trial ^[39] 29:4 42:15 79:6,7 86:1,4 87:12 90:21 98:18 118:7 163:3,11 172:3 174:8 227:4 240:2 256:11 266:7 272:19 273:11 275:22 279:16 281:8 282:6 284:8 285:9,13 299:4 315:10,12 324:2,7 336:21 338:19,20 357:1 377:6,17 380:4 Trials ^[82] 15:4 16:18 17:5,17 19:2,19 20:7 26:5 28:9 32:3,6,9 34:10 77:2 80:3 84:9 90:</p>	<p>10 92:18 94:5 100:16 116:19 117:4,8,10 120:2,15,16 121:2,20 126:11 129:12,19 134:21 136:2,10 138:12 162:21 163:17 174:13 177:12,13 183:13 226:10 240:3 253:2,21 255:21 259:9,20 260:18 261:19 262:2 267:2,13,22 268:18,20 270:13,18 271:1,4,19 272:22 273:7 274:14 276:5 279:12 280:4 282:2 285:7,8 286:17 288:7 290:16 292:14 293:19 339:21 357:7 372:6,14 376:8 381:12 tricky ^[1] 241:14 tried ^[3] 152:20 360:4 372:3 trigger ^[1] 24:2 triggered ^[1] 101:19 triglyceride ^[1] 92:6 triglycerides ^[7] 67:18 78:12 83:9,18 164:20 253:9 297:6 tripled ^[1] 82:12 trivial ^[1] 343:12 trouble ^[1] 240:22 troubled ^[2] 319:21 370:21 troubles ^[1] 357:13 trough ^[1] 57:3 TRPV1 ^[1] 59:14 true ^[17] 19:11 26:20 27:20 55:11 57:14 64:4 107:20 113:14,15 173:17 248:22 258:9 287:6 295:7 303:14 325:19 371:21 try ^[11] 5:8 10:15 145:15 243:4 247:8 312:7 322:16 357:8,14 363:22 369:19 trying ^[12] 22:15,17 71:3 154:1 238:5 249:20 330:3 347:6 360:21 367:22 370:5 380:19 tumor ^[1] 226:5 turn ^[2] 186:6 256:2 turned ^[1] 133:13 turns ^[1] 376:22 Twenty ^[2] 74:20 110:12 Twenty-three ^[1] 163:4 twice ^[2] 206:16 227:12 two ^[89] 12:6 14:2 26:7 46:16 53:20 54:22 61:16 75:19 76:2,4 80:10 85:16,22 87:16 89:20 90:3,15,21 100:2 103:12 107:10 114:11,15 115:1 117:9 120:8 122:3,4 124:15 126:18,22 128:7 130:7 131:6 132:4,14 133:15,15 150:11 154:3 161:21 163:2 170:15 171:3,18 174:20 178:12 179:14 183:17 187:21 195:21 216:11 222:13 230:13 232:8,21 234:13 238:13 246:20 256:22 257:5 259:16 265:6,10 266:13 267:14,16,21 274:17 289:6 294:12 301:3 309:11 310:2 311:7 314:16 319:5 321:13 327:4 328:10 330:20 337:9 338:18 353:9 365:3 368:16 370:2,13 374:5 two-fold ^[1] 270:6</p>	<p>two-point ^[1] 149:21 two-sided ^[1] 149:5 two-thirds ^[3] 63:22 104:7 309:13 two-year ^[4] 84:9 204:17 240:2 364:20 tying ^[1] 305:12 type ^[47] 37:5 39:15 41:14 43:19 44:10 45:10 50:3,7 61:19 62:1,3,5 65:15 68:7,17 69:13 70:3,5 72:17 74:3 76:12 81:1 85:15 87:14 88:18 91:20 92:9,21 93:18 95:21 138:22 163:11 168:15 169:9,17 218:19 244:9,13 245:9 253:6,10 265:9 300:17 306:9 319:1 330:6 331:18 types ^[5] 21:12 35:12 107:10 163:16 328:10 typical ^[3] 29:19 197:2 228:22 Typically ^[2] 54:19 308:6 typo ^[3] 248:18,19,19</p> <hr/> <p style="text-align: center;">U</p> <hr/> <p>U-shaped ^[1] 196:7 U.K ^[1] 376:16 U.S ^[7] 63:2 69:21 70:4 117:6 152:19 244:15 278:18 uh ^[1] 35:3 UK ^[7] 44:5,21 144:8,11 155:20 156:2,14 ultimately ^[1] 298:18 unadjudicated ^[1] 309:11 unanswered ^[1] 232:1 unapproved ^[1] 74:5 unbalanced ^[1] 259:18 unbiased ^[1] 21:7 unblinded ^[1] 133:13 uncategorized ^[1] 303:17 uncertainty ^[1] 298:9 unclear ^[4] 117:14 253:14 297:17 342:1 uncomfortable ^[1] 353:19 unconfirmed ^[1] 267:19 uncontrolled ^[2] 115:21 239:15 under ^[28] 47:16 87:18 95:20 103:8 110:11 113:1 172:22 189:2,16 199:14 200:18 201:11 208:7 211:20 214:18 220:8 242:6 252:4 255:13 276:8,9,10 278:15 305:1,3,18 307:5 308:21 undercounting ^[1] 181:17 underestimate ^[3] 258:8 277:14 281:13 underestimates ^[1] 300:12 underestimating ^[3] 350:13 358:22 366:17 underestimation ^[1] 313:8 underlying ^[4] 158:22 159:20 265:2 275:13 underrepresented ^[1] 300:8 underscores ^[1] 162:14 understand ^[17] 97:7 155:8 178:1 200:19 222:21 236:13 247:3 249:7 317:19 319:9</p>	<p>331:21 338:7 351:3 357:7 358:1 370:15 375:7 understanding ^[11] 32:17 67:4 69:14 171:11,19 192:1 196:12 231:18 246:22 334:22 340:15 understands ^[1] 249:6 understood ^[4] 189:10 192:18 244:6 317:16 undertaken ^[1] 335:3 undertaking ^[1] 246:3 underutilized ^[1] 161:22 underway ^[1] 381:13 undesirable ^[1] 200:2 undetected ^[1] 102:5 uneasiness ^[1] 261:16 unequivocally ^[1] 57:17 unexpected ^[1] 55:21 unfamiliar ^[1] 53:19 unfortunately ^[5] 67:2 71:4 235:3 329:17 354:20 unilateral ^[2] 304:20 375:13 unintended ^[1] 55:20 Union ^[2] 45:6 144:10 unique ^[9] 48:17 151:19 194:13 254:5 255:8 302:22 380:19 381:17,18 United ^[9] 44:17,18 45:3 69:19 143:18 146:5 157:17 234:11 293:12 University ^[10] 6:21 7:1,9,17 8:3 37:15 49:4 283:1 303:6 329:15 unknown ^[6] 22:13 229:14 233:10 266:21 282:8 298:10 unless ^[4] 300:1 319:20 322:22 335:8 unlikely ^[4] 131:7,14 133:2,16 unmasking ^[1] 268:21 unopenable ^[1] 338:5 unproven ^[1] 298:15 unrealistic ^[1] 71:6 unrestricted ^[1] 243:13 unscheduled ^[3] 289:10,15,19 unscrupulous ^[1] 237:8 until ^[7] 5:19 196:14 238:10 251:4 371:20 372:9 377:2 untoward ^[1] 171:17 untreated ^[3] 66:9 76:10 83:3 unusual ^[1] 116:5 up ^[59] 20:12 22:8 26:8,10 27:21 56:14 67:1 70:8 74:3 84:22 92:3,7 106:18 114:7,9 124:20 134:6 161:14 170:10 181:14 182:4 183:15 204:16 222:13 227:8,11,11 229:12 230:13,22 239:17 240:1,19 241:9,22 254:4,15 260:19 265:20 268:19 293:21 295:17 296:5 305:12 306:9 310:3 311:6 318:22 337:4,17 347:2 349:2 351:5,5 356:22 367:14 372:21 378:16 379:11 update ^[3] 18:13 45:19 185:1</p>
---	---	--	---

<p>updated ^[4] 45:14 128:15 264:15 271:2 upon ^[13] 10:7 147:19 150:16 196:3 197:14 198:20 208:3 250:5,6 343:10,19 367:12 382:22 upping ^[1] 376:2 upset ^[1] 238:2 uptake ^[1] 67:18 urge ^[1] 242:19 urged ^[1] 181:5 us ^[48] 10:20 11:10,13,19 14:2 21:4 30:7 32:14 35:4,17 41: 19 48:7,9,14 52:7 59:7 65:12 112:6 144:15,16 151:2 155:8 184:20 224:6 237:9,9 243:4 258:22 261:15 264:22 307: 15 308:14 311:12 315:17 319:9 320:4 322:1 327:9 329: 21 338:8,10,13 345:1 368:19 372:10 377:3 381:9 382:21 use ^[60] 11:2 32:2 46:18 50: 6 54:11 56:5 74:5 89:10 122: 15 133:18 136:6 137:21 139: 6 140:10,13 142:18 145:4 146:1 151:1,11 156:18 159:9 161:11,15,22 164:15 167:19 182:13 215:5 226:9 232:13, 18 233:15 238:13 240:1 258: 9 270:18 273:10 274:8 287: 20 297:10 298:10 312:9 314: 20 315:2 316:11,12 326:15 334:4 335:15 344:10 348:18 349:2 357:6 359:7 363:22 364:18 365:1 377:3 used ^[41] 11:4 20:3 23:3 47:3 57:10 60:22 65:19 73:20 90: 21 91:5 111:11,13,17 114:4 115:8 142:19 143:17,19 149: 20 153:14 161:10 167:1 196: 5 206:13 224:4 229:10 231: 21 254:19 260:7 276:3 284:4, 6,11 285:14 286:6 295:6 300: 7 304:14 305:1 306:14 317: 13 useful ^[3] 60:1 65:11 73:14 users ^[1] 313:18 uses ^[2] 31:13 238:13 using ^[30] 26:13 32:9 45:4 56: 7 59:1 74:22 80:1 83:4 89:17 101:21 111:8,13,15 114:4 115:17 116:11,12 121:7,10 130:1 136:8 155:18 172:7 225:19 233:2 254:21 264:15 278:6 304:12 363:5 usual ^[3] 320:13 322:13 377: 16 usually ^[9] 29:20 34:18 87:6 104:16 123:13 217:9 304:7 334:13 371:7 utility ^[3] 138:5 146:2 382:9</p> <p style="text-align: center;">V</p> <p>vague ^[2] 268:16 339:15 valid ^[2] 68:16 321:7 validate ^[1] 312:6 validated ^[3] 91:5 149:21 150:4</p>	<p>value ^[1] 228:13 values ^[2] 172:22 227:6 vanilloid ^[1] 194:17 variability ^[1] 20:18 variable ^[1] 360:12 variance ^[3] 324:19,22 332:1 variation ^[1] 44:11 varied ^[3] 77:21 256:11 257:8 variety ^[9] 51:9 52:9 186:16, 20 189:14 195:1,21 204:12 256:6 Various ^[19] 31:13 51:10 94: 13 146:4 186:9 193:22 194: 15 205:12,13 208:2,5 210:7 247:10 262:6,21 283:4 295: 12 314:20 340:11 vary ^[1] 307:20 varying ^[1] 290:3 vascular ^[1] 59:20 vasoconstriction ^[1] 60:5 vast ^[2] 261:15 303:16 vehicle ^[1] 63:15 vehicle-treated ^[1] 66:16 verbalization ^[1] 288:4 verbally ^[1] 241:1 verbatim ^[2] 123:3 302:10 versa ^[1] 305:13 versatile ^[2] 188:13 193:20 version ^[1] 29:6 versus ^[52] 55:11 66:16 83: 11 86:3,5 88:8 98:20 99:6 119:22 121:17 124:21 125:8 131:1,6,21 132:18 133:5 222: 10 226:21 250:7 259:5,13 261:13,20 262:11,15 263:10, 12 264:4 270:3 275:18,20 277:6,18,19,20,21 279:1,4,22 280:18 281:8,11 285:21 292: 22 313:18 315:1 340:13,14 344:11 345:10 347:7 vertigo ^[4] 268:14 301:15 302: 2 303:15 very ^[164] 10:20 13:16 14:13, 16 16:17 19:6 23:12 24:17 25:6 27:3,12 29:18,18 33:3, 13 34:12 35:7,11 53:2,10,10 55:4,8 56:4,14 58:20 59:9 75: 14 76:14 80:10 87:18 95:10 103:13 104:1,8,14 106:5 116: 1 117:13,14 118:8 119:11 120:4 123:14 125:17 126:15, 21 130:2 132:8 133:20,22,22 134:11 135:16,20 136:1 137: 13 143:2 144:22 149:19,19, 20 150:20 151:1 156:21 157: 3,13,18 168:8 171:4,13,15,16 173:22 175:2 177:16 183:10 184:17 194:5 205:16 212:8 230:16 231:5 234:8 236:14 237:12,13,20 238:2 239:22 240:21 242:12 243:1 245:7 265:14 285:17 286:7 301:4 303:19 314:9 315:13 316:9 319:18,22 320:21 321:9 324: 6 325:2,3 326:22 327:11,17 329:16 331:7 332:5 333:10, 16 334:3,9 340:9,10 341:6,10 342:1,4 344:17 346:2,2 347: 16 350:17,18 351:21 352:7 353:19 354:2 356:7 360:20 362:2,8,22 363:7 364:14,16, 19 365:21 366:3,4,9 370:4,9, 12 371:2,3,17 372:1,10 373:2 377:1,1 379:10 380:1,7,10 381:10 vesicles ^[2] 51:1 188:7 via ^[5] 43:14,21 94:22 117:12 192:4 viable ^[2] 170:1 231:4 Vice ^[4] 36:21 69:2 93:3 305: 13 view ^[7] 41:17 67:3 91:14 108: 1 143:22 258:7 347:15 viewed ^[1] 277:13 viewing ^[1] 184:16 views ^[1] 246:14 Vioxx ^[2] 224:16,18 virtue ^[2] 180:14 328:9 visceral ^[2] 61:20,22 vision ^[2] 266:11 301:18 visit ^[5] 34:2 98:8 119:4 153: 18 358:20 visited ^[1] 118:14 visits ^[7] 152:9 270:17 289:10, 12,13,15,19 visual ^[2] 262:21 268:14 vitro ^[4] 52:19 57:20 88:15 218:19 vivo ^[2] 52:18 57:20 vocalize ^[1] 288:2 voice ^[1] 289:12 voltage-gated ^[1] 192:20 voluntary ^[2] 143:7 182:12 vomiting ^[4] 99:1 127:20 128: 1 297:19 vote ^[25] 327:4 336:3 337:22 338:1 342:18 351:16 353:22 354:1 355:19,21 358:9,14,15 362:1 364:9 365:17 367:16 372:11,21 383:5,7,7,11,11 384:21 voted ^[2] 385:1,1 votes ^[2] 385:2,2 Voting ^[3] 2:4,10 337:14 vulnerable ^[2] 110:14 129:15</p> <p style="text-align: center;">W</p> <p>W ^[2] 2:8,20 waist ^[4] 81:12,14,16 92:5 waivers ^[1] 8:21 walking ^[1] 301:15 Walter ^[1] 303:5 Wang ^[17] 2:17 7:12,12 300: 21 307:14,15 308:2,12,17 354:3,4,8,8 356:1,3 384:7,8 want ^[43] 27:1 31:10 106:10 117:16 121:8 146:15,17,18 151:9 153:2 156:7,7,9 177: 20 178:1 181:11 235:20 238: 14 240:20 241:10 242:21 300:1 312:16 321:13 323:13 327:15 339:1 345:8 349:17 351:7 356:10 358:9 365:4 367:21 370:6,12,13 371:3 374:13 376:12 377:22 380:2,</p>	<p>4 wanted ^[24] 15:14 19:20 21:7 24:9 29:10 112:20 153:4 181: 17 182:6 219:16 235:15 237: 10 294:11 296:12 299:17 318:22 323:22 332:6 333:4 343:2,22 347:1 358:16 374: 12 wanting ^[3] 24:16,16 174:17 wants ^[3] 216:9 237:21 242: 18 warning ^[3] 183:21 184:3 287:8 was ^[388] 15:16 17:21 18:1 19: 3,11,12,16,22 20:3 21:1,21 22:3,20 23:12 24:22 25:9,10 26:4 30:15 33:19 35:7 38:13 39:2 43:13,14 44:5 45:4,5,8, 12 50:14 51:17 52:8,16 56: 18 58:10,21 63:20 68:17 75: 4,8,9,19 76:11,14 77:19,22 78:6,11,15 79:2,3,8 80:2,4,4, 4,10 81:21 82:4,16 83:5,21 84:7,14 85:5,5,10,20 86:1,4, 10,11,16,22 87:22 88:2 89:12 91:2 94:12 95:16,17 96:6 97: 4 98:10,20 99:3,6,15,20 100: 15 101:7,14 102:3,8 103:4 104:4,6,8,9,21 105:15,17,19, 22 107:2,15,20 109:13,21,22 110:1,10,16,20 111:14,16,17 112:17,18 113:14,15 114:20 115:4,7,22 116:20,21 117:11, 17 118:4,7,22 119:4,6,7,8,9, 11,17,20 121:15,19 122:2,7 123:12,15,17,19 124:19,20 125:1,2,3,8,10,21,22 126:5, 12,15,15 127:8,9,11,15 128:3, 3,11,15 130:5,11 131:1 132:7 135:12,17,18 136:16 144:9 145:6,8 146:14 148:12 158:5 163:9,10 167:6 175:19 176:2, 12,18 177:4,9,16 178:20,21 179:2,7,22 180:2,5,10,22 181: 4,7,8 182:7,14 183:7 204:10 205:2,6,7 207:9 218:21 219: 2 220:17 224:3 226:1 229:16, 17,18 230:16,18 233:3 234:4 238:4,22 239:21 240:1 241: 19 242:10 246:21 248:16 249:7,19 252:4,22 253:5 254: 3,18 255:9,16,18 256:4 257: 22 258:22 259:1,5,12 262:12 263:13 264:5,18,21 265:8 266:5,6,8,13,15,17,18,20,21 268:5 269:4 271:8 273:11 274:21 275:17 278:7,7,17 279:6,10,22 281:20,21 282:6, 13,17,17 284:7,11,13,13 285: 15 287:16 288:15 289:21 291:17 293:19 294:11,17,18 300:5,18 301:6 302:18,19,21 305:8,8,11,12 306:8 308:9,14, 15,22 309:20 312:1,15 313: 12 315:9,14,17 316:3,10,22 317:3 318:5,9 319:12,14 320: 12 321:8,9,18 322:12,12,15,</p>
---	--	--

<p>18 323:5 325:2,7,8,11,19 326:11,15 327:14,16 333:8 336:17,19,20 338:5,6,10 339:4,12,14 344:17 346:8 347:11 348:18,20,22 350:15,19 352:4,7 355:7 357:7 358:18 360:7,21 365:13 367:6,14 368:11,16 372:13 373:15,15 374:1,3 375:9,11,11,12,12 380:11,12,21 385:21</p> <p>Washington ^[1] 8:5</p> <p>wasn't ^[4] 316:7 318:6 321:9 323:15</p> <p>waste ^[1] 326:7</p> <p>watch ^[2] 334:3 353:10</p> <p>way ^[45] 19:1 23:16 27:21 29:7 30:17 34:1,2 35:5 36:2 55:13 56:2 57:16 79:21 105:13,22 111:9 135:9 136:4 145:13 151:16 156:21 161:8 164:10 169:11 173:3 177:3 208:16 258:16 297:3,4 334:19 335:14 336:17 337:10 359:7,18 367:7,14 372:15 373:5 374:1 376:1 378:5 383:10 385:11</p> <p>Wayne ^[4] 2:14 7:16 356:4 373:12</p> <p>ways ^[4] 18:17 233:7 350:2 359:9</p> <p>We ^[576] 5:7,8,15 6:2 8:10 9:1,10 10:3,9,14,21 11:16,21,22 12:5,5,8,17 13:16 14:7,10,19 15:11,17 16:10,13 18:18 19:19 2:4,15,17,17,18,19,20,21 20:6,17,19,19 21:6,15,17,20 22:4,4,8,10,18,19 23:16,17,18 25:8,8,9,17,20 26:1,6,22,22 27:8 28:21,21 29:2,2,6 30:2,3,4,10,13,18,21 31:6,9 32:2,21 33:21 34:1,15,16 35:11,13 36:10,10,11 37:3,8 38:8,13,21 39:11,19 40:13,15,17 41:2,2,4,15 42:4 44:7,16,20 45:3,9,20,22 46:2,4,8,11,21,22 47:10,18,19 48:7 53:20 55:12 57:18 65:8 81:11 82:10,21 83:14 89:10 90:21 91:5 94:1,9,18 95:9 96:10 98:3 100:21 101:5,7,9 102:9 111 104:19 105:13,21 107:9 108:2,7,13 109:3 110:2,22 111:7 112:11,20,22 114:2,2,4 115:8,14 117:1,7 120:4,18 121:7,10,12 123:22 124:20 126:17,18 128:16 129:13,18,20 130:10 132:4,5,15,16 133:3,4 134:1,2,10,12 135:5,6 136:4,7 137:1,3,4 139:20,21 140:9,15,17,18,21 141:4,13,17,18 142:1,21 143:1,5,9,12,14,15,15,17,19,21 144:2,12,13,18,22 145:7,13,17,21 146:1,1,2,7,14,15,17,18 147:9 148:6,9,12,14,22 149:1,3,17,19 150:13,16 151:1,6,9,12 152:12 153:2,4 155:4,14,20 156:2,2,6,7,7,9,10,14,16,18 157:9 158:7,19 159:22</p>	<p>160:16,17 161:12,20 162:7 163:16 164:12,22 165:12 166:11 167:7,18,19 168:16 169:17 171:4,9 172:4 174:7 179:8,13,15 180:8 181:13,14,21 182:18,20 184:5,9,12,16,21,21 185:3,6,8,13 190:15 191:10,21,22 194:8 200:19 202:3,7,15 211:19 215:1 217:4 218:22 219:4 220:5,7 221:5 222:3,5,7,11 223:17 224:15 226:8 228:3,20,22 234:16 235:3,4 236:2,3,5,6,10,10,14 237:7 240:21 242:13,22 243:12 245:15,17 246:2,9,18,19 247:2 249:3,7,20 251:2,22 257:4,14,19 258:6,6,18 263:20 265:6,19 267:15,16 271:8,14 272:22 276:11 277:9,12 278:3,10 279:3,13 285:14 286:3,5 287:11 291:9,18,21 292:6,7,13,17 293:22 294:2,7,11,14 295:20 296:11 297:1,19 298:4 299:21 300:2,16,19 302:17,20 303:2,21 304:12,19 305:10 306:9,12,12 307:12,21 308:3,9,10 309:8,16,19 310:6,7,12,14,17,17,18,20,21 311:15,18 312:6 313:13,13,15,16,20,22 314:3,11,12,17 315:11 316:4,5,7,8 318:1,9 320:2,4,11,17 321:4,12 322:5,7,10,18 323:7 325:4,22,22 327:2 328:18 329:9,21 331:2,13 332:13 333:5,17 334:2,4,6,10,12,13 335:7 336:1,1,11,11,12,12,22 337:2,4,6 338:4,12,14 339:6,6,7,11,19 341:1,10 342:3 344:19 345:8,19 346:7,16 347:8,14,20 348:4,5 350:12 354:9,10 356:21 358:3,21 359:1 362:17,22 364:9,16,18,19 365:2,12 366:8,17,19 369:10 370:14 371:13,14,15,15,20,21,22 372:6,9,19 373:1,6 374:14 375:5,5,18,19 376:5,14,15,20 377:13,15,15,16 378:5,6 379:10 381:1,4,4 383:5,6 385:3,13,15</p> <p>weak ^[1] 380:7</p> <p>weakness ^[2] 268:15 301:18</p> <p>weaknesses ^[1] 255:3</p> <p>wealth ^[1] 379:19</p> <p>web ^[1] 151:13</p> <p>website ^[3] 230:22 250:20 251:4</p> <p>websites ^[1] 353:3</p> <p>Wednesday ^[1] 1:7</p> <p>week ^[8] 74:21 75:3 117:20 118:16 225:17 250:22 287:4 294:3</p> <p>weeks ^[13] 63:8,16 66:4,4 75:11 76:22 114:22 115:1 118:9 134:6 167:6 259:11,11</p> <p>weigh ^[1] 363:15</p> <p>weighing ^[1] 166:15</p> <p>Weight ^[225] 4:9 11:2,4 13:4</p>	<p>61:11 63:10,11,17,22 64:3 67:5 68:8 69:16 71:4,4,6,9,11,15,16 72:6,9,16,20 74:5,8 75:13,16 77:21 78:4 79:14 80:3,10,11,17,20 81:1,4,5,11,14,17 82:1,2 84:11,22 85:2,3,11 86:10 87:5,11,20 88:7,12 89:3,8,12,16,18 90:1,6,13,16 91:22 92:4,9,13 103:6 111:21 137:12 138:19 148:5 154:10,11 157:22 158:22 160:1,4,13,17 161:3 162:15,17 163:10,12,14,15,20,21,21 164:9 165:4,5 168:13 169:4,6 171:20 172:1,2 174:15 175:7,8 176:4,5,7,8,11,15,19,20,22 177:3,8,9,15 182:9 190:5 200:11 201:4,8 203:7 212:8,21 213:6,19 232:12 234:4,12 235:10 236:1,16,17 237:22 238:16 241:16,20 242:1,4,9 244:16,20,21 252:10,11,14,22 253:7,16 254:11 278:13 279:2 291:2,5,10,12,17 297:5,6 298:12,14 307:18 308:22 309:4 314:5 321:16,21 322:10,13,15,17,19 324:22 325:2 326:5,10,13 330:9,12,14,16,21 331:10,20 332:3,11,11,21 333:1,2,8 337:4 343:15,16 344:10 345:11,20 348:9,20 353:15 357:17 359:12,13,15,21 360:1,9,15,16 361:15 363:1,20,21 364:1,2,4,6 370:20 373:17,19 379:2 382:17,18,20 383:17</p> <p>weight-control ^[1] 252:6</p> <p>weight-independent ^[3] 348:14 349:1 360:18</p> <p>weight-loss ^[9] 252:7,20 253:5 254:7 279:4,7 294:13 328:20 363:5</p> <p>weight-management ^[1] 251:18</p> <p>weights ^[1] 174:16</p> <p>welcome ^[3] 5:3 15:2 36:14</p> <p>well ^[79] 14:15 16:5,9 19:16 21:1 25:10 26:9 27:14 31:2 35:10 40:19 44:8,13,21 45:16 46:1,17 50:16 55:6 57:1 75:5,13 76:12 86:17 91:20 92:5 96:9 105:18 109:8 121:14 135:4 138:20 148:15 151:10 152:12,18 153:5,14 154:20 157:21 161:20 165:3 178:15,22 183:9 187:10 189:10 191:1 192:17 193:16 195:2,20 196:4 204:20 228:12 243:14,19 254:8 256:11 264:20 272:20 284:17 295:8 303:13 315:7 327:8 333:15,20 343:18 347:18 357:15,18 358:7,7 359:5 374:13 377:9 379:10 380:16</p> <p>well-being ^[1] 244:15</p> <p>well-defined ^[1] 16:13</p> <p>well-studied ^[1] 241:17</p>	<p>went ^[20] 22:1 23:16 102:9,11 106:18 108:22 114:7 130:10 227:8,11 230:12 241:21,22 279:15 318:6,7,10,12 337:11 341:6</p> <p>were ^[303] 20:6,13,15,20 22:15,17 23:3 24:10 25:1,4,6,12,15 26:7,9,9 27:5,7 28:8 39:6,8,9,20 63:14 64:9 65:14,18,20,21 66:11,12 74:21 75:12,13,14 76:6,15,18,20 77:2,10,14,15,17 78:19,19,21 79:9,15 84:1,9,17 85:1 86:1,20 87:13,18,19 92:7,15,17 94:7,22 95:7 96:11,13,14,20,22 97:1,3,14 98:6,18 99:11,12,13 100:2,7,8,13 101:3 102:16 104:1,10,14,20 105:7 106:16,19 107:8 108:7 109:9,20 110:3,7,12,12,15,18 111:10 113:8,19 114:21 115:1,2,10 118:1 120:8 122:9,18 123:8 124:9,16 125:17 128:11 129:7,10,12,13 130:7,16,16,17 131:6,8,12,12,13 132:2 133:11,14,16 134:1,7 136:11,19 146:14 154:3 163:7 175:16,21 176:13,17 180:6 181:5,14 183:15 184:8 203:7 204:14,18 205:22 206:3,4,13,14,15 207:2 208:10 209:1 210:3 211:13,15 216:16 217:13,14,15 218:2,6,7,16,17 221:8 224:16 231:5,10 232:8 237:4 238:17 239:20 247:4 250:17,18 253:15 254:11 255:20 256:11 257:10,11,13,17 258:12 259:6,8,16,19 260:4,7,9,10,18,19 261:11,17,17 262:7 263:20 266:11 267:21 270:12,17,22 271:6,9 273:10 274:13 275:3,4,5,11 276:2,12 277:2,10,16 279:11 280:3,19,22 281:4,5,14,17 283:1,11,17,19 284:6,15 288:6 289:5,9,13,16 290:9 295:2 300:7,10,14 304:12,13,20,21 305:1,5,5,18,22 306:10,14,16 308:20 309:11 311:12,22 312:8 313:4,4,6 316:5,8 318:1,15 319:3 320:11,15,19 321:2,5 323:6 324:20,21 326:3 333:6 334:7 339:21 341:17 342:1 346:2,3,4 355:6 358:20 360:5 362:11 365:8,14 367:3,20 368:9 370:22 371:1</p> <p>weren't ^[7] 22:7 206:2 218:9,22 271:14 362:15 372:5</p> <p>what ^[194] 6:5 12:20 13:9 15:11 16:16,18 17:3,6 18:16 19:15,22 20:6,7 21:1,17,19 22:1,3,4,19 23:18 25:4,8 26:3 27:2,12 30:22 31:9,20 34:11 35:8 38:21 42:1 53:20 58:14,19 65:2 70:10 72:1 73:2,17 87:6 91:13 106:12 112:20 120:22 125:19 130:22 133:13 142:17,18 143:7 145:14,17 146:</p>
---	--	--	--

13,14,15 147:9 148:1,4,21,22 149:3,17 152:17,17,21 153:1, 6 154:7 155:2,9 156:11 157: 2 164:18 166:11 171:21 172: 22 173:20 174:2,20 185:3 195:5 197:3 212:20 217:4,6 219:21 232:3 234:21 237:2 239:16,20 240:6,10 242:14 247:12 248:11,15 264:20 280:9 282:8,8 287:16 293:19 294:9,11,12,14,21 297:1 301: 12,20,21 303:17 304:10 306: 3,13 307:7,10 309:14 311:15 314:21 318:1,9 319:9 320:20 322:12,18 325:7,13 327:9 329:18,19,20,20,21 330:8,16 331:9,22 332:3,12 333:9,17, 18,18,20 336:1,11 337:1,19 340:16 342:1,2,2,6,9 343:2 345:8,14 346:7 347:6 348:13 349:11,17 350:4 351:2,5 352: 20,21 353:2 354:4 356:1 358: 4 361:11 369:1 370:13,21 372:21 373:10 374:13,17 375:1,10 376:5,7 378:6,12,16 380:11 381:3,13 385:7 whatever ^[8] 89:22 110:19 131:5 179:20 228:19 241:12 334:17 335:5 when ^[83] 11:4 13:6 18:11 20: 17 21:6 24:8,10 26:7 27:16 28:14,15 31:3 43:20 51:13 56:14 57:13 58:12 66:4 77:9 84:22 85:8,9,18 87:7 102:5 104:9 105:2 106:16 111:18 115:15,15 122:2 126:17,22 131:20 132:2 161:3 165:16 170:2 172:1 173:22 174:22 175:7,19 179:15 205:6 234:4 235:5 236:10,17 237:6 239: 10 241:18 243:18 263:10 279:7 287:18 301:13,14 305: 3 319:16 324:9 325:5 330:12 333:7 343:5 346:8 349:22 351:2 357:14 359:7 360:18 361:12 364:14 366:14 371: 14 372:6 374:6,18 375:19 379:7 382:16 383:18 whenever ^[1] 377:2 Where ^[46] 16:8,8 22:20 45:3, 9 56:3 60:19 61:2 63:13 64:9, 15 77:15 86:12 94:16 96:18 111:10 114:16 115:7,18 116: 20 130:9 132:15 149:6 168:4 184:1 216:4 224:16,20 226: 10 228:10 235:2 245:10 257: 9,12,16 272:9 287:3 302:18 312:1 313:18 315:9 356:10, 19,20 360:3 382:17 whereas ^[3] 106:22 356:16 359:16 whereby ^[1] 331:5 Whereupon ^[2] 221:7 385:21 whether ^[36] 22:3 34:14 35: 13 63:18 89:7 104:4 110:9 116:4 123:15 147:16 152:5 171:9 181:3 227:22 239:3	271:10 286:5 299:14 300:18 305:10 309:17,19 317:12 321:20 324:5 325:14 344:18, 19,20,21 348:1,6 353:4 357:4 359:21 368:13 which ^[183] 5:14 9:21 13:15 19:10 20:2,22 25:5 32:21 33: 2 35:21 37:9 39:1,4,21 40:8 41:9 46:9 48:1 51:21 54:3 55: 10,11 56:13,18 57:4 58:16 62:16,17 64:10 66:2 67:22 73:20 80:2,8 87:16 91:2 97: 10 101:7 103:13 106:4,11 107:13 108:16 109:19,21,22 111:16 114:3,7 115:8,11 116: 14 120:4 123:12 130:2,16 134:2,10 136:14 141:9,13,14, 17 143:17 144:13 145:7 146: 3,7 148:18 150:14 151:13 152:9,20 153:11 157:9 158:6, 18 159:1 161:14 162:10,21 164:12 168:19 172:6 177:3,4, 22 179:9 182:22 183:14 185: 4,9,20 186:16 187:15 188:4 189:1,11,19 190:6,15 191:10 192:3,7,22 193:3,11 200:5,9, 14 205:8 208:14 209:7 210: 20 217:14,15 219:21 224:22 226:12 232:13 233:7,21 234: 10,11 235:18,18,21 236:4 241:19 248:7 252:6 258:19 262:14 263:5,14 264:14,21 265:13 266:10,12,17 268:12 271:4 272:19 276:12,15,17, 20 282:16 283:15,18 284:7, 22 285:6 286:1,21 289:15 296:2 297:19 302:3,10 307:2 311:7 313:15 314:9,19 325:7 326:17 330:4 333:8 341:3 344:6 345:15 348:17 351:8 359:7,18 360:11 362:10 368: 18 371:1 376:20,21 whichever ^[1] 366:15 while ^[18] 33:10 55:20 59:1 60:3 66:11 87:10 88:11 91:1 162:16 165:4,12 185:1 219:4 232:12 233:4 237:19 261:10 270:1 white ^[1] 55:7 who ^[151] 5:10 11:5,19 12:2 13:18 14:4,5,19 34:9 39:12 42:21 46:19 47:1,11,13,21 48:3,4 49:3 52:7 59:7 81:22 84:20 91:19,21 93:3 96:11, 13,22 97:1 102:13,14 104:13 107:22 109:1 115:1 117:21 118:15 127:19,22 128:12 130:8 137:5 138:20 143:12 144:14,19 147:12,12,12,15 150:21 157:3,7,20 166:1 167: 14 168:1 169:12 170:5 172: 20 173:4 174:3 176:17 177:2 180:11,20 181:2,22 184:21 223:17,20 224:4,6 233:3 237: 21 239:11,18 240:12 242:17, 22 245:9 252:12 254:17,18 257:5,19 266:5 267:22 268:3,	6,20 275:11 277:10 279:11, 21 280:1,6,11 281:4,5 287:22 288:11 290:12 291:5,13 293: 7 309:21 312:11 313:4 314:4 317:14 318:1,4,11,17 319:3,5 320:5 321:11,20 326:3 327:8 332:20,22 333:12 338:6 339: 8 340:12 341:8 343:7 344:3 350:20,21 352:22 354:17 356:22 358:2 359:11 363:5,9, 11,18,20,21 368:14 375:9 376:4,8 380:3 382:11 whoever ^[1] 371:8 whole ^[16] 17:11 23:11,11 80: 18 232:5 239:7 262:21 281:5 305:5 332:19 334:3 335:10 336:12 359:1 377:5 378:11 whom ^[6] 144:15 282:7 320: 15 334:16 355:4 363:12 whose ^[3] 10:6 281:16 288:3 why ^[16] 13:9 29:15 32:21 84: 8 114:10,11,11 174:21 175:7 292:11 306:12 317:19 345: 13 355:7 357:7 372:5 wide ^[2] 126:15,21 widely ^[2] 191:15 231:19 widespread ^[2] 51:19 232:11 wildfire ^[1] 353:3 will ^[274] 5:10,13,14,17 6:2 8: 9,10 10:2,15 11:7,10,16,19, 21,22 12:2,8,17 13:22 14:19, 20 16:3 33:2,9,11,11 36:14 37:1,8,9,12,17,20 38:8,22 39: 5,18,19 40:8,10,13 41:16 42: 4 44:6,7,15,16,22 46:1,21,22 47:10,18,19,21 49:2,20,21,22 50:4 53:20 55:3,12,19 56:17 57:9,10 60:3,5 65:8 69:4,11, 14 74:15 79:17 87:15 89:19 93:17,21 94:1,8 95:8,9,19 97: 6,7,10 98:3,11 100:21 101:7, 9 108:2,18 112:11 121:4,7,10 129:5 130:19 135:5,6 136:7, 7 138:10,14 139:21 140:7,8, 15,17,18 141:9,12,14,18,22 142:1,2,6,9,12,14,18,19,20, 21 143:1,8,12,16,18,18,21 146:1,1,2,7,7,10 147:20 148: 2,6,10,14 149:1,1,5 150:14, 16,20 151:1,7,12,13,21 152:5, 7,9,12 153:10,15,16,19,20 154:4 155:3,4,6,8,10,12 156: 2,18,22 157:16 170:11 182: 18 183:2 184:10 185:6,7,8,10, 13,21 186:2 187:13 191:10 200:12,13 207:6 212:14 215: 17 221:5 222:3,4,5,7 223:15, 19 225:1 230:21 232:15 235: 4,21 236:19,20 237:1,2,14,18 238:21 246:9,11,18 247:2 250:19,20 251:12,16,18 256: 2 258:11,17 273:2 280:11 282:9 294:15 298:1 301:2 308:9 311:5 312:6,7 323:1, 14,20 324:7 327:3 328:17 329:8 332:9 333:1,3,11 334: 1,16,16,18,18 335:14 336:1,1	338:14 340:1,7 343:2 348:2, 7 349:17 352:20 356:17 359: 18 361:20,21 365:1 368:14 374:11 376:2,13 377:19 383: 10,12 willing ^[2] 316:6 337:6 wind ^[1] 356:22 window ^[1] 271:5 wish ^[7] 10:7 30:18 35:14 36: 1,2 243:12 356:20 wished ^[1] 25:1 with ^[517] 5:16,18,22 6:1 8:22 10:3,6 11:7,17 12:3 13:4 14: 2,4,6,11,19 17:12,19,20 18: 15 20:3,12 21:13 22:12 23:8, 19 24:8,18,19 26:18,22 27:18 31:16,17 34:14 38:3,14,15,22 39:10,20 40:11 42:9 43:9,18, 22 44:7 45:9 46:12,18 47:4,4, 13,15 48:7,9,21 49:8,17 50: 11 53:5,9 55:5 56:20,20 59:3 60:11 61:22 62:19 63:1,6,14 64:10 15 65:20 66:8 68:7 69: 3 70:6 71:9 72:7,22 73:9,15 74:7,11,15,21 75:10,19 76:7, 9 77:8 78:2 79:10 80:12,20 81:2,5 82:4,17 83:3 84:2,3 85:8 86:2 89:16 90:20 91:3, 15,17,17 92:9,13 93:12 94:3, 10,17,17 95:18 96:7,8 97:15, 17 98:21 22 99:1,3,6,13,18, 20,22 100:1,3,3,9,15 101:10, 13 102:10 103:22 104:1 105: 3,8,17 106:3,11,13,16 107:1, 8,19 108:2,4,13,21 109:10,13, 17 111:21 113:8,17 114:3,9, 15 116:13,19 117:6,22 118:3 120:7,8,10,16,19 121:21 122: 3,8,19,20 123:3,18 124:3 125: 15 126:3,5,13,21 127:19,22 128:1,15 129:6,7,8 130:15,22 132:12,19 134:9,14,16,16,22 135:1,13,13,14,19,20,21 136: 5,13,16,19 137:18 138:1,10, 22 139:16,19 140:3,10,11 141:2,16 142:5,17,20 143:2, 13,20 144:3,5,8,13 145:4 146: 3,15,22 147:2,13,19 149:2 150:10,15,16 151:17 152:20 154:15 155:6,13 157:4,13 158:14 159:4,8,11,13,14 160: 10,20,20,22 161:11 162:9,11, 11,17,18 163:12,15 165:16, 21,22 166:5,8,9,21 167:5 168: 2,9,17 169:5,7,7,17 170:13, 20 171:16 172:21 173:7 174: 9 175:5 176:20,21 178:19 179:2,16 181:15 182:13,16, 17 185:13,22 186:9 190:1 193:10 195:6,9,9,11 197:19 198:3 199:9,12,18,22 202:13, 15 204:3,15,18 207:19 208: 19 209:10,14 210:19 211:11, 19 213:19,19 214:4 215:10, 22 216:5,8 220:18 223:5,9 224:3,6,13 226:6 227:10,15, 20 228:16 229:14,15 230:5,7
---	---	---	--

<p>232:22 233:8,14 234:16 236:14 238:22 239:15 240:2,22,22 241:10 245:2,4,9,12,14,18 248:16 250:2,21 251:13,17 252:10,21 253:4,6,10,19 254:6,7 255:5,9,19 258:9 260:1,4 263:4 265:13 266:4,7 267:3 268:6,11,12,16 269:17 270:5,6 272:6,18 273:8,22 274:8 278:15,21 279:12 280:2,12 281:1,21 282:8 284:17 288:3,5,13 290:15 293:3 295:19,19 297:10 298:17 301:2 302:17,20 304:1,7 305:11 306:9 307:1,7,10 309:6 313:9 314:3 315:10 316:18 317:4,5 318:9 319:15 320:4,22 322:7,11 323:18 326:1 328:22 329:21 330:12,22 331:3,6,17 332:2,12,17,19 333:6,15,20,21 334:7 339:20 340:15,17 341:5,20 342:5,10 344:20 345:2 346:16 348:18 349:10,16 350:11 352:4 353:6,14,20 354:4,11 355:9,15 356:1 358:4 359:19 360:10,13 361:20 364:3 365:16 366:12 367:20 368:6,7 369:5 370:4 371:15 372:2,3 373:7 374:3 375:9 376:6,8 378:3 381:5,12 382:16 383:12,17 385:12,16</p> <p>withdrawal ^[1] 253:21</p> <p>withdrew ^[1] 254:3</p> <p>Within ^[23] 31:13 32:15 36:22 37:1 44:10 46:6 118:3 128:5 160:4,7 166:19,22 167:8 225:2 250:21 257:10 268:7 270:16 275:1 283:5 294:3 296:6 340:21</p> <p>without ^[24] 38:15 47:6 84:2,3 85:2 86:4 107:11 111:14 116:11 131:3 138:4 165:13 185:12 254:14 304:2 321:15 324:2 332:13 335:3 341:1 348:19 360:12 377:4 380:15</p> <p>Witness ^[1] 119:10</p> <p>Wolfe ^[6] 4:3 223:18,22 224:1,1 235:7</p> <p>Wolpaw ^[1] 224:6</p> <p>woman ^[4] 70:8 128:14 268:6 333:13</p> <p>women ^[10] 61:18 310:10 323:6,7 362:22 363:13,14 365:8,10,14</p> <p>Women's ^[1] 298:16</p> <p>won't ^[6] 109:19 181:19 236:21 305:16 354:5 383:13</p> <p>wonder ^[4] 319:8 321:16,20 376:18</p> <p>wondered ^[3] 180:12 217:22 344:18</p> <p>wonderful ^[4] 331:7 334:7 335:6 381:19</p> <p>wondering ^[4] 33:19 180:10 313:2 323:7</p> <p>Woody ^[2] 380:20,20</p> <p>Woolf ^[25] 2:18 6:17,17 220:</p>	<p>10,10,15 249:12,12,16 250:3 300:22 308:20 311:10,18 326:2 336:9,9 337:17,19,22 339:3 340:3 369:20 377:9 383:20</p> <p>word ^[3] 304:2,9 353:3</p> <p>wording ^[2] 103:14 150:20</p> <p>words ^[4] 301:19 340:10 342:10 380:14</p> <p>work ^[10] 15:15 16:3 59:7 91:8 161:19 225:8 230:1 335:13 377:18 381:4</p> <p>worked ^[4] 152:6 203:7 372:2,3</p> <p>Working ^[4] 108:21 157:13 373:7 385:16</p> <p>works ^[3] 370:17,18 381:18</p> <p>world ^[1] 18:10</p> <p>worldwide ^[3] 114:19 135:1 139:7</p> <p>worried ^[2] 312:8 332:15</p> <p>worrisome ^[4] 264:7 265:19 362:8 367:5</p> <p>worry ^[6] 334:14 351:4 359:6 361:11,13,18</p> <p>worse ^[4] 178:16 236:4,12 359:10</p> <p>worsened ^[1] 118:3</p> <p>worsening ^[1] 118:18</p> <p>worst ^[1] 22:19</p> <p>worth ^[1] 25:10</p> <p>would ^[205] ^[1] 5:20,22 9:1,10 10:16,17 13:13 14:7 16:2 25:1 31:1,10 32:11 33:16,17,20 34:2,8 35:19 42:11 44:17 49:15 53:14 57:5 58:11 68:18 69:1 71:11 89:21 90:19 93:2 120:22 128:8 132:11 134:14 135:9 136:14 137:8 140:3 148:18 149:7,15 152:2 157:19 158:13,15 161:20 163:12 165:12 166:6 169:8,11 170:13 176:9 178:14 180:13,15 181:6,9 183:1,6 184:13,17 197:4 199:14 203:12 205:19 212:13 214:19 228:3 229:12,12 232:4 233:22 234:3,21 235:3 238:6 240:17,17 241:1,3,9,9 242:8,19 248:9 249:5 250:13 251:4 275:19 279:18 284:1 289:1 290:12,21 291:18 292:16 297:1 299:3 306:2,6 307:6 308:17,18 309:17 313:8 314:5 315:14 316:13 317:11 318:20 319:9 320:20 321:3,21 324:11 325:14,17 326:9 327:1 329:11,12 331:8 332:5 335:4 336:5 337:4,22 338:1 340:4 341:1 342:18 343:7,20,21 345:4 346:16 348:21 350:8 351:14 352:5,12 353:13,14,15,19,21,22 354:1 355:19,21 356:20 357:2 358:12,12,14,15 359:8,10,13,16 360:9 362:1 363:11,15 364:1,9,9 365:3 368:17 369:10 371:2,2,3 372:4,11,18,20,</p>	<p>22 373:8,20 374:2,13,16 375:1,3,17 376:5 377:18 378:10,12 379:17,21 380:1,2,4,10,17 381:5,19 383:2 385:6,9,19</p> <p>wouldn't ^[3] 217:16 296:3 335:14</p> <p>wound ^[1] 119:2</p> <p>wrap ^[1] 181:14</p> <p>wrapped ^[1] 18:6</p> <p>wrist ^[3] 22:14,15,17</p> <p>write ^[1] 20:13</p> <p>written ^[5] 18:11 103:19 223:3 314:13,17</p> <p>wrong ^[4] 24:6 139:14 338:8 365:13</p> <hr/> <p style="text-align: center;">X</p> <hr/> <p>X ^[1] 360:12</p> <hr/> <p style="text-align: center;">Y</p> <hr/> <p>Yale ^[2] 8:3 217:21</p> <p>Yeah ^[1] 316:16</p> <p>year ^[54] 13:20 33:10 39:3 66:7 72:20 77:9 80:3,12 84:17,19 85:3 96:8,13,14,15,20 97:3 126:13 131:16 135:3 139:6 148:9 151:8 156:12 163:2 169:7 175:10 183:15,17 204:16 217:1,10 232:9 234:9 253:22 254:2 256:22 293:4 294:17 295:14 296:6,19,19 309:16 311:1,3,6 330:20 338:18,20 352:20 368:19 370:2,2</p> <p>years ^[47] 14:8,12 23:15 27:12 32:2 40:1 61:7 77:5,8 84:11,22 92:7 94:18,19 96:12 97:19 117:4,5 128:4,17,21 131:17 134:20 158:3 163:3 217:1,7 232:8 238:22 241:21 257:1,5 272:4,5 294:14 311:7 323:8 327:14 336:18 338:19 365:3 367:1 368:5 371:6 374:5,6 381:22</p> <p>yellow ^[5] 54:2 65:20 106:15,17 291:14</p> <p>Yes ^[39] 35:22 150:7 174:7 176:3,10 180:4 181:16 216:10 219:14 220:15,16 249:15 250:5,10,14 302:22 303:22 306:9 307:21 308:2 310:2 313:12 314:2 315:6,22 316:10 325:17,19 329:14 346:20 347:1 354:8 356:1,1 358:15 373:13 377:12 383:9 385:2</p> <p>yesterday ^[3] 294:4 337:19 353:15</p> <p>yet ^[18] 17:20 18:2 60:20 71:20 86:22 148:22 170:22 171:4,15 224:11 297:9,22 300:9 311:21 315:12 358:3 364:20 367:9</p> <p>yielded ^[1] 114:6</p> <p>yielding ^[1] 116:13</p> <p>York ^[5] 9:13 14:22 15:1 158:1 329:15</p> <p>you ^[573] 8:8 10:8,13,21 12:7,17,18 13:1,17,20 14:13,18 15:7,10 17:12 18:9 19:3,6 20:2,</p>	<p>9,17,19 22:7,12,20 23:4 26:7 27:21 28:14,15 30:9 31:18 32:5 33:15,16,20 34:1,2,5,5,13,16 35:6,8,10 36:1,3,9 37:7,9,9 38:22 39:5,19 40:11,13 41:4,20 42:2,14 43:9,16,20 44:6,12,22 45:21 46:1,12 47:19 49:12,16 51:12 53:9,19 54:6 55:10 56:3,14,16,17,19,21 57:6 58:6,11,13,14 61:19 62:22 63:15 64:16 68:20,22 75:15 84:16,20 86:2 88:14 90:20 92:22 93:1,8,11 95:19 97:6 99:11 100:14 103:21 105:3 106:12,14,16,17,18,19 108:8,8,9,10,11,17 121:8,8 122:12 126:17,22 130:19 131:18,20 132:2,13,16,17,19,22 133:4,6,7,7,17,18,18,19 134:8 137:10 140:1,2 141:14 142:14 143:19 144:6,8 145:8 149:6,22,22 150:4,21 152:20 156:4 157:18 164:3 165:16 166:18 170:6,9,10,10 171:6 173:8,10,22 174:17,18 175:1,3,12 177:1,12,18 178:5,8,11,13,16 179:5,11,16,19 180:4,10,16 181:14,17,19 182:11,18,21 183:2,19 184:9 185:1,5,19 187:2,18 189:20 192:14 194:21 196:3,19 197:8,13,14,14 198:12 199:1,3 200:12 201:19,20 202:5,11 203:5 205:14,15 206:5,6,7,19 208:22 209:2,6,9,19 210:11,16,17 212:14,20 215:13,14 216:1,4,12 217:16,18 218:8,9,12,13,14 219:3,5,11,16,21 223:1,4,11,12,13,16,19 224:13 225:1,18 226:2,13 229:1 230:2 234:3,6,21 235:1,6,7,16 236:7,13,17,17,21 237:15,16,19 238:2,18,21 239:10,11,21,21 240:13 241:6,7,8 242:19,21 243:3,5,6,10 246:13,15 247:3 248:6,9,11 249:19,21 250:2,11 251:1 252:1 256:6,18 257:2 258:7 262:12,17,18,20 263:13,19 264:5,17 265:11,12,17 269:20 271:18 272:2 279:5 280:10 281:3 283:1 285:12,17 286:4,6 287:14 289:22 290:2,4,8 292:2 294:15,15,20,21 295:4,5,5,11,16 296:3 300:1,3,3,11,14 301:2,7,21 302:5,16 303:13,19,20 304:10,11,14 305:14 306:9 307:1,6,7,9,10,10,15,19,21 308:5,11,13,13 311:5,12,16,21 312:6,20 313:15,17 314:2,21 315:3,4,16 316:1,13,13,14,17 317:8,20 318:14,19,22 320:7 321:2,6,22 322:6,21 323:13,21,22 324:3,5,9 325:5,14,20,21 326:3,22 327:8,9,11,22 328:13 329:11,18 330:1,19 333:7,7,13,22 335:16,18,18,22 336:5</p>
---	---	--	--